ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 14 March-April, 1956 Number 2

ANTIGENIC ANALYSIS AND STANDARDIZATION OF TRICHINELLA EXTRACT BY GEL DIFFUSION

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A SURVEY of the literature indicates that trichinosis is a disease with a strong hypersensitivity factor.[2,14] It may be accompanied by transferable reagin[7] and its symptoms are mediated by potent antigens.[10] The disease may be recognized by the detection of antibodies in the patient's serum by flocculation,[2,9,26] complement fixation[28] and precipitin,[4,6,25] and in the patient's skin by intracutaneous test.[4,25] Either the delayed or immediate type of reaction, or both, may be encountered, the delayed preceding the immediate by several days in the development of the disease.

Oliver-González[18,19] has shown that rabbits infested with trichinella develop two types of antibody, one directed against the adult worms and one against the larvae. On the other hand, animals sensitized by injection of an extract of trichinella larvae develop antibodies only against the larvae. Aikawa et al[2] state: "It is also possible that the antigenic components of immature unencysted trichinella larvae may also be slightly different from mature encysted forms."

Of the various tests employed in the diagnosis of trichinosis, all appear to suffer from lack of complete specificity. It has been reported that *Ascaris* antigen frequently cross reacts with trichinella;[3,7,8,10] thus it has been argued that the two nematodes must contain common antigens.[7] *Trichinella* has frequently been found to cross react with *Trichuris trichiura*.[15] Patients with trichinosis have occasionally been found to react to typhoid bacilli and *Proteus* x 19[27] and with agents of various

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Presented in abstract, as The use of Gel Diffusion Techniques in the study of Allergens, at the Eleventh Annual Congress, American College of Allergists, Chicago, April 27, 1955.

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other diseases.[6] On the other hand, Aikawa et al[1] state that "cross reactions between trichinella and other parasites at low dilution (1:100) tend to disappear at higher dilutions (1:10,000). . . . It is not known whether the cross reactions are associated with a polysaccharide or with a protein fraction."

Besides its lack of specificity, a disadvantage of the cutaneous test is that a large proportion of the test subjects become sensitized to the trichinella antigen, 33 per cent after three to five tests, 56 per cent after nine tests.[3,7]

Melcher and Campbell[17] prepared a purified polysaccharide by extracting the dried ground larvae in saline, adjusting to pH 8 and by boiling for fifteen minutes. The polysaccharide was precipitated by alcohol and purified by repeatedly redissolving and reprecipitating. It was shown to be a good skin reacting and precipitating antigen and did not cross react with *Ascaris* or with other helminths. Its antigenic properties were not destroyed by autoclaving at pH 7 for fifteen minutes at 15 pounds of pressure. Witebsky et al,[28] using this same antigen, which they called Antigen E, found that the removal of other substances by boiling the extract largely reduced the nonspecific reactions without greatly lowering the specific potency of the extract.

Melcher[16,17] isolated two biologic fractions from trichinella larvae, an acid soluble protein and a polysaccharide. The former consisted of three electrophoretic components and elicited intradermal and precipitin reactions in rabbits; the latter showed precipitin reactions only. Neither fraction was found to cross with *Ascaris*.

These antigens were further investigated by Frisch and associates,[13] who found that the unpurified saline extract gave 25 per cent immediate and 33 per cent delayed skin responses. "The acid-soluble protein was distinctly less reactive, and the polysaccharide proved to be practically inert." And they state, "It is believed that the major component of *Trichinella spiralis* larvae responsible for intradermal and complement fixation reaction is heat stable and precipitable by alcohol and acetone."

Portwood and Sanders[23] found that by heating a saline extract of trichinella larvae to 58°C for one hour, or acidulating to pH 4 in the cold, about 80 and 70 per cent, respectively, of the material could be removed with very little alteration in the electrophoretic patterns or their antigenic activity.

Aikawa et al[1] found that peptic and tryptic digestion of trichinella did not destroy its antigenicity for dogs by skin tests nor its flocculation test with sera from infested animals, suggesting that the antigenic fraction is not solely protein but might be partly carbohydrate.

Avera et al[5] considered the possibility of the false positive reactions occasionally obtained with trichinella being due to the ingestion of pork containing killed trichinella larvae. Hogs fed cooked trichinous meat over a period of weeks gave weakly positive intracutaneous reactions to trichinella

extract without becoming infested, but the authors were unable to reproduce this phenomenon in guinea pigs or rabbits. They consider the question still unanswered.

Frisch et al[13] have pointed out the need for a reliable method of standardizing trichinella extracts. They suggest that "the material could be standardized by intradermal means and against serums from known cases of trichinosis for skin, precipitin, and complement fixing activity." This brief survey of the literature has revealed no serious attempt to standardize the antigenic potency of trichinella extracts.

By means of the gel diffusion technique it is possible to test the effect on the antigenic pattern of such agents as heat, acid, proteolytic or other digestions. One may also compare trichinella extract with those of other related and unrelated forms, and determine if there are common or even similar antigens among them. It is also possible to detect trichinella antibodies in human sera and to standardize the extracts against a standard antigen or antiserum.

MATERIALS AND METHODS

Trichinella larvae were removed from infested rat muscle by peptic digestion, thoroughly washed with saline, followed by distilled water which apparently killed them, and dried by sublimation. The dried material was weighed and extracted in phosphate buffered saline, pH 6.8, 1 gm to 200 ml. The extraction was continued for forty-eight hours in a ball mill, with toluol as preservative. The insoluble material was removed by centrifuging. The extract was preserved with 0.5 per cent phenol and sterilized by filtration.

Antisera were prepared in rabbits as already described,[29] injecting the larval extract, 1:200, combined with an equal volume of Freund's adjuvant.[12] The animals were given two injections of one ml each, twice a week for six weeks. All animals responded by developing antisera of unusually high titer, so were bled out after a second series of injections.

For antigenic analysis the double diffusion method of Ouchterlony[20] was used with the reactants placed in penicillin cups resting on the surface of plain agar. For quantitative study the Oudin[21,22] technique was used. The serum was combined with agar, poured into flocculation tubes and overlaid with the fluid extract.

Antigens.—

Tr. *Trichinella spiralis* extract, 1:200 except where otherwise stated.
Rat ser. Normal rat serum undiluted.
Dip. *Dipylidium caninum* extract, 1:200.
Pig Asc. *Ascaris lumbricoides* var. *suum* extract, 1:200.
Dog Asc. *Toxascaris canis* extract, 1:200.
Typh. Typhoid vaccine, 73 billion per ml.
Par. A. Paratyphoid A vaccine, 94 billion per ml.

Par. B. Paratyphoid B vaccine, 59 million per ml.
Sk. Streptokinase 5 pts + Streptodornase 1 pt.

Antisera.—

P. 36. Antitrichinella rabbit serum developed by injection, pool of three bleeding from each of two rabbits.

Ser. 238. Antipig ascaris serum from injection, first bleeding from a single rabbit.

P. 39. Antistreptokinase serum developed by injection, pool of two bleedings from each of three rabbits.

G.P. Guinea pig antitrichinella serum from infestation, concentrated three times.

Bat., deF., R.T., J.T., H.G., R.M. human sera from known cases of trichinosis, all concentrated three times.

EXPERIMENTAL STUDIES

Precipitation Patterns.—When trichinella extract is allowed to diffuse against antitrichinella rabbit serum, at first there appear two precipitation bands. After five days (Fig. 4) these are well defined and characteristic. No. I, closest to the serum source, is rather faint and diaphanous, and not sharply defined except sometimes on its proximal edge. It has a bluish cast, especially its proximal half which may be partially separated, showing a lack of homogeneity. It is strongly arched about the serum source. The outer band, No. II, at this stage is more opaque, narrower and longer, and shows the blue color only as a narrow streak along its proximal edge and at the two ends where it projects slightly beyond the colorless precipitate, suggesting that this band is also composite. It is less arched than Band I, in keeping with its greater distance from the serum source. It is a characteristic tendency of precipitation bands in general to form in hyperbolic

LEGENDS FOR ILLUSTRATIONS

(See opposite page)

Fig. 1. Trichinella heated momentarily to 100°C compared with the same material unheated, diffusing against their homologous antiserum, appearance after about one month.

Fig. 2. Trichinella extract acidulated compared with the same material unacidulated. As in Figure 1, after thirteen days.

Fig. 3. Trichinella extract compared with rat serum diffusion against antitrichinella serum, after twelve days.

Fig. 4. As in Figure 3 but after five days.

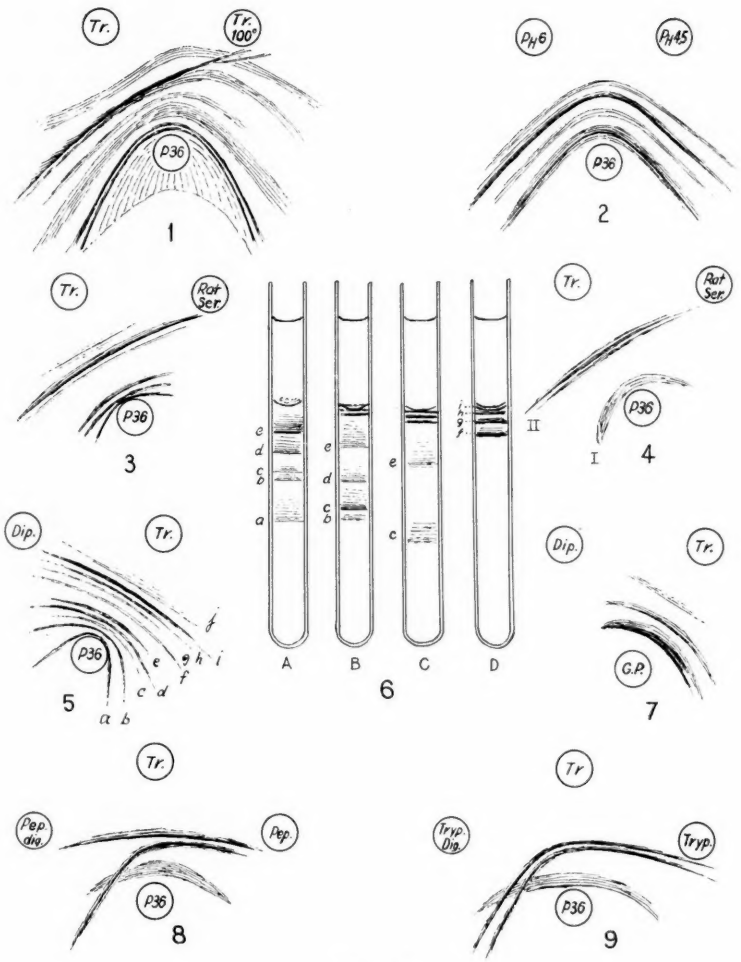
Fig. 5. Dipylidium and trichinella extract compared diffusing against the antiserum of the latter, after about fifteen days.

Fig. 6. Trichinella extract, 1:500, diffusing into mixtures of equal parts of agar and antisera of various concentrations. A. 1:1, B 1:2, C. 1:4, D. 1:6, after twelve days.

Fig. 7. Dipylidium and trichinella diffusing against the serum from a trichinized guinea pig, three times concentrated, after about fifteen days.

Fig. 8. Pepsin-digested trichinella extract compared with undigested material. Pepsin (Pep.) is used for control, appearance after ten days.

Fig. 9. As in Figure 8 but with trypsin digested material.



Figs. 1-9

curves, arching toward their nearest reactant source, and when formed midway between the two sources they tend to be straight lines.

When the trichinella extract or its antiserum or both are weak, these two bands may be all that develop, as if only two not quite homogeneous antigens were involved. However, if the reactants are strong, with further diffusion each band separates into three, as in Figure 3, which is its appearance after twelve days. Under favorable conditions it may proliferate as in Figure 5, which is its appearance after fifteen days. Ten bands are in evidence. The first five, *a-e*, derived from the original band I, the next four, *f-i*, from the original band II, and a dissociated band *j*, appearing to

have originated later than and independently of either. It is uncertain whether these should be regarded as representing ten separate antigens or only three, two of them heterogeneous. With the data presently at hand it seems best to regard them as representing two unrelated groups of closely inter-related antigens, and a single dissociated one.

Of the bands of Group I, *a, b* and *d* have a distinctly bluish cast, suggesting by analogy with ragweed[33] that they represent antigens composed largely of polysaccharide. This accounts for the bluish appearance of the group as a whole. Of Group II only band *g* is bluish, accounting for the generally whitish appearance of the group as a whole. This group is dominated by band *i* which is opaque white and is the most prominent of all, suggesting that it represents the major antigen.

A similar arrangement of bands is obtained in single diffusion tests in Oudin tubes (Fig. 6). In this the serum in a series of dilutions was incorporated in the agar and trichinella extract allowed to diffuse into it. With the strongest serum (tube A) the five antigens of Group I pass into the serum phase, but those of Group II do not. At this concentration their antibodies are in excess, moving in the opposite direction and forming unorganized precipitates in the liquid antigen phase.

When the serum is diluted by one-half (tube B), the antigens of Group II begin to penetrate the serum phase and the bands of Group I begin to disappear because of antigen excess (actually antibody deficit). At a dilution of 1:6 (tube D) all bands of Group I have disappeared while at least four of Group II have established zones of equivalence in the antibody phase. Thus all of the precipitation bands seen in Figure 5, except one, are accounted for. The missing band is probably *j* which is extremely faint and not always seen even in the Ouchterlony plates. It may be formed in the interphase boundary or be concealed by the trailing zone of its heavy preceding band.

Control Tests.—Since the trichinella extract was prepared from the larvae encysted in rat muscle, it was necessary to examine the extract for rat antigens. Normal rat serum was compared with trichinella extract diffusing against antitrichinella rabbit serum (Fig. 3). The rat serum formed no precipitation bands nor did it turn any of the trichinella bands. The experiment was repeated using an extract of normal rat meat with the same results, showing the absence of sufficient host antigen in the trichinella extract to produce antibodies.

EFFECT OF HEATING TRICHINELLA EXTRACT

The extract, pH6.9, was heated to 58°C in a water bath for one hour, then kept refrigerated overnight. No visible precipitate was formed. This was compared with the unheated material diffusing against antitrichinella serum (Fig. 30). Every band interferes forming symmetrical arches, the pattern of identity. The two fractions were also compared for activity by

the standardization technique to be described later, and found to be of identical potency.

The same material was heated momentarily to 100°C then cooled. Another fraction was boiled for thirty minutes. When these were compared with the unheated fraction (Figs. 1 and 31), it was seen that all the antigens of Group I remained unimpaired, since their precipitation bands form symmetrical arches with those of the unheated control. But of Group II the major antigen is completely destroyed. Two of the minors persist, one of them in a weakened form shown by its displacement toward the antigen source. The lower one of these has a distinct bluish cast identifying it with the *g* band in Figure 5. Antigen *j* appears to be unaffected by heating to 100°C.

When heated still higher, autoclaved at 20 pounds pressure, about 126°C. for one hour (Fig. 32) all antigens, except that of one band of Group II, were destroyed.

EFFECT OF ACIDULATION

Trichinella extract was adjusted to pH 4.5 by the addition of strong HCl. A slight precipitate was formed which was removed by centrifuging. When the supernatant was diffused against the antiserum in comparison with the same material unadjusted (pH 6.9), all bands interfere forming symmetrical arches (Fig. 2), showing that this degree of acidity has no effect on the antigenicity of the extract.

EFFECT OF PROTEOLYTIC DIGESTION

Trichinella extract, 1:200, was made alkaline (pH 8.7) by adding normal NaOH, trypsin added and incubated at 37°C for forty-eight hours. A similar portion was adjusted to pH 1.9 with HCl and digested with pepsin at 48°C for twenty-four hours. For controls, the same material was diluted by the same amounts with saline. The digested fractions were then compared with their controls and with their enzymes trypsin and pepsin (Figs. 8 and 9). It is seen that neither of the enzymes *per se* has any effect on the precipitation pattern, but trypsin removes all of the antigens of Group I without affecting those of Group II, while pepsin removes all antigens of both groups except the same one that survived autoclaving.

That these results were due to proteolytic digestion alone and not to the alkaline and acid treatment was demonstrated by adjusting the extract to pH 8.7 and pH 1.9 and repeating the experiment. The adjustment of pH had no significant effect.

ANTISERA OF INFESTATION

The serum from a guinea pig that had developed trichinosis through being fed trichinized rat muscle was diffused against trichinella antigen. The serum used was concentrated three times from the lyophilized state,

and the antigen at 1:200 dilution. After eight days two faint precipitation bands appeared. Later these became more intense and a third faint band appeared nearer to the antigen source (Fig. 7). The band closest to the serum source showed a distinctly bluish color and with two well marked blue streaks, probably identifying it with Group I. The second band, somewhat narrower and denser was white with only a bluish streak along its proximal edge, probably identifying it with Group II. The third was extremely faint and is identified by its character and position with band *j*.

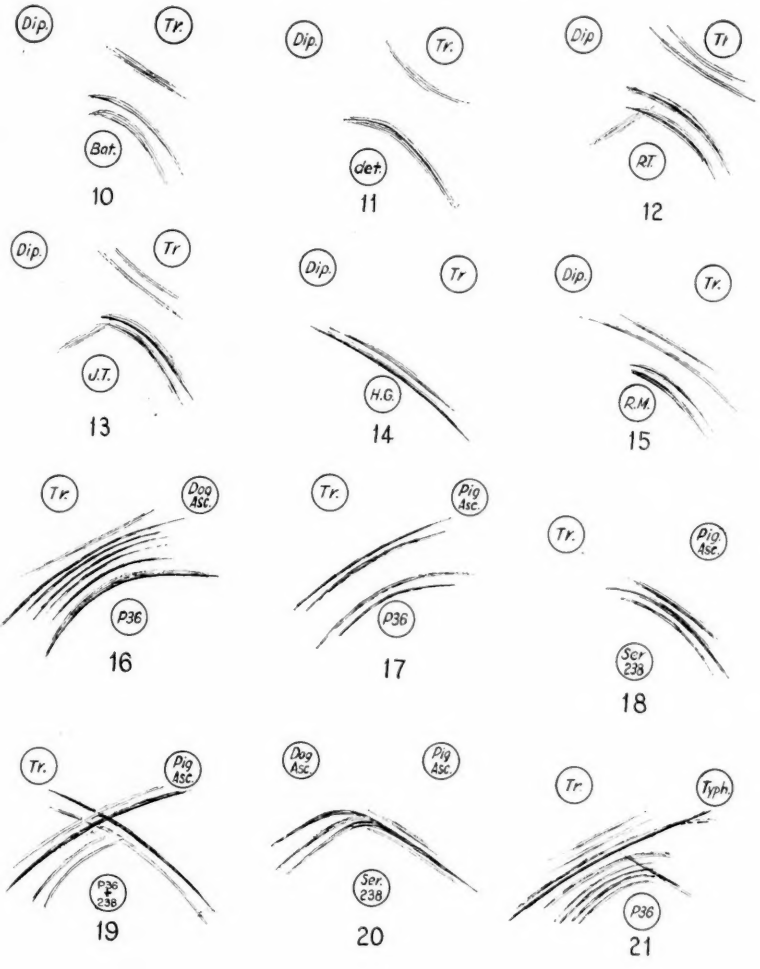
Similar experiments were tried with the sera of six known human cases of trichinosis, also used three times concentrated. Of these, the one designated "Bat.", obtained from a convalescent case, was found to give satisfactory passive transfer skin tests at a dilution of 1:10. The others which appear to have been taken from active cases of trichinosis, failed to transfer even when used undiluted.

In gel diffusion tests (Figs. 10 to 15) all gave one or more precipitation bands. The Bat. serum, though strongly skin sensitizing, gave neither more nor stronger precipitation bands than the other sera, showing that the skin sensitizing and precipitating antibodies are different and not correlated.

Control experiments done with normal human serum in place of the trichinous sera proved negative. Moreover, this was also true when pooled human gamma globulin was substituted for the trichinosis serum, showing that the development of the precipitating antibodies is contingent upon infestation by *Trichinella*. It also shows that in the general population along the Atlantic seaboard, where the gamma globulin was obtained, neither the incidence of subclinical infestation nor ingestion of killed trichinella larvae is sufficient to engender antibodies to them as suggested by Avera et al,[5] notwithstanding that the same batch of gamma globulin had been shown to have high reaginic titers for ragweed and timothy pollens.

When human antiserum Bat. was compared with rabbit antitrichinella serum diffusing against trichinella antigen (Fig. 27), Bat. serum formed two precipitation bands which eventually fused, one with the major and one other band of the outer group and one with the dissociated band of the rabbit serum, thus establishing the identity of the corresponding antibodies in the two sera. Also the ends of the other bands of the outer group were more or less turned by Bat. serum, denoting the presence of common antibodies in lesser amounts. But the inner group of bands from the rabbit serum remained unaffected, denoting only subminimal amounts, or total absence, of the corresponding antibodies in Bat. serum.

The other four human sera from cases of trichinosis tested in the same way all gave similar patterns, for example, de F. (Fig. 28), while normal human sera, proved to be completely negative. This shows that human sensitization from trichinosis is more closely associated with the antigens of the outer precipitation bands than those of the inner group.



Figs. 10, 11, 12, 13, 14 and 15. Dipylidium and trichinella extracts compared diffusing against the sera from trichinosis patients, all concentrated three times, after fifteen days.

Fig. 16. Trichinella and dog-ascaris, diffusing against antitrichinella serum, after twelve days.

Fig. 17. Trichinella, 1:200, and pig ascaris, 1:50, diffusing against antitrichinella serum, after sixteen days.

Fig. 18. Trichinella and pig ascaris, both 1:200, diffusing against antipig-ascaris serum, after nine days.

Fig. 19. Trichinella and pig ascaris diffusing against their combined antisera, after about seven days.

Fig. 20. Dog ascaris compared with pig ascaris diffusing against antipig-ascaris serum, after about nine days.

Fig. 21. Trichinella compared with typhoid vaccine diffusing against antitrichinella serum, after twelve days.

CROSS REACTIONS OF TRICHINELLA

In some of the above experiments, both with antisera of injection (Fig. 5) and of infestation (Figs. 10 to 15), there was included an extract of *Dipylidium caninum.* It was used here as a representative of the cestode parasites which have been reported[11,24] to cross react freely among themselves. The extract was prepared in essentially the same way as that of trichinella. In the diffusion tests the dipylidium antigen always slightly deflected at least part of the inner group of bands. With two sera (Figs. 12 and 13) dipylidium formed a band of its own. The fact that all these antitrichinella sera, including that of the guinea pig, react slightly to dipylidium suggests that there is a slight cross reaction between it and trichinella, but the reactions of R.T. and J.T. sera (Figs. 12 and 13) suggest that these patients may have had some cestode infestation as well as trichinosis. Moreover, both types of cross reaction are associated primarily with the antigens of the inner group of precipitation bands.

When trichinella was compared with *Ascaris lumbricoides* var. *suum* (pig ascaris), the latter failed to produce any precipitation bands with antitrichinella serum (Fig. 17) and trichinella failed to produce precipitation bands with antiascaris serum (Fig. 18). Nor did either interfere with the other's precipitation bands, except for a slight turning of the end of the inner ascaris bands by trichinella (Fig. 18). When diffused against their combined antisera (Fig. 19) their precipitation bands crossed almost without interference in the pattern of nonidentity.

When trichinella was compared with *Toxascaris canis* (dog ascaris) diffusing against antitrichinella serum (Fig. 16) the dog ascaris formed no precipitate nor interfered with that of trichinella. On the other hand, when dog ascaris and pig ascaris were compared diffusing against antipig ascaris serum (Fig. 20), they formed patterns of partial identity showing all antigens to be common or closely similar in the two species, but occurring in different proportions.

Various human antisera, including four of the antitrichinella sera mentioned above, one pollen-sensitive and one from a case of hydatid cyst, when diffused against pig ascaris extract, were all completely negative. This was also true of pooled human gamma globulin. This would make it seem probable that the many supposed cross reactions reported between trichinella and other nematodes might have been due to subclinical infestations by parasites other than trichinella. With more closely related members of the group, such as the dog and pig ascaris, cross reactions can be expected.

Trichinella extract was compared with typhoid, paratyphoid A and B vaccines diffusing against antitrichinella serum (Figs. 21, 22 and 23). In all three cases the bacterial antigens turned the proximal ends of Group I trichinella bands. This is most marked with Typhoid and Paratyphoid B. Also these latter both formed precipitation bands of their own. These do not interfere with any of the bands of the trichinella patterns, showing

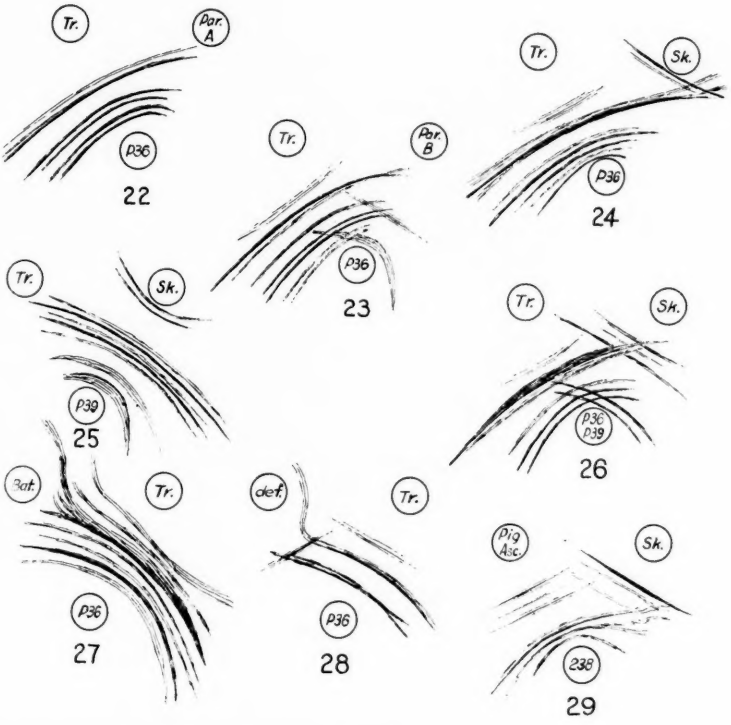


Fig. 22. As in Figure 21 but with paratyphoid A.

Fig. 23. As in Figure 21 but with paratyphoid B.

Fig. 24. Trichinella compared with streptokinase diffusing against antitrichinella serum.

Fig. 25. As in Figure 24 but with antistreptokinase serum.

Fig. 26. As in Figures 24 and 25 but diffusing against their combined antisera.

Fig. 27. Serum from a human case of trichinosis (Bat.) compared with rabbit antitrichinella serum diffusing against trichinella extract, appearance after eighteen days.

Fig. 28. Serum from a case of human trichinosis (de F.) compared with rabbit antitrichinella serum diffusing against trichinella extract, 1:500, appearance after eleven days.

Fig. 29. Pig ascaris, 1:50, and streptokinase diffusing against antipig-ascaris serum undiluted, appearance after nine days.

nonidentity. Such bands must be regarded as of heterophile origin. Similar bands have been recorded with Bermuda grass and timothy[32] and are apparently quite common among bacterial antigens, as suggested by the following experiments.

Trichinella was compared with streptokinase diffusing against antitrichinella serum (Fig. 24). Streptokinase slightly turned the proximal ends of the *Trichinella* Group I bands and formed two heterophile bands

of its own, which crossed the major *Trichinella* band without interference. When the same two extracts were compared diffusing against anti-streptokinase serum, the trichinella antigen neither turned the bands of the streptokinase nor formed bands of its own (Fig. 25). In this case the

Fig. 30. Trichinella extract unheated (left) compared with the same material heated to 58°C. for one hour (right) diffusing against their homologous antiserum, appearance after about one month. The assay cups were removed from the agar plates of this and the two following figures, for purposes of photography. The former position of only the serum cup shows distinctly. The two antigen cups were above in the usual triangular arrangement.

heterophile bands of streptokinase can be recognized by their position and appearance. They form close to the antigen source and have a distinctly bluish color, especially the proximal one. They thus form indifferently with the homologous or heterologous antiserum. When these two antigenic extracts were compared diffusing against their combined antisera (Fig. 26), the bands of both systems were seen to cross without interference, including the heterophile bands, but at the same time the bacterial antigens turn the bands of trichinella but not the reverse. It is thus seen that streptokinase carries heterophile antigens that react freely with trichinella antibodies, also that their antigens are similar enough to those of the trichinella inner group to interreact slightly with them. Both properties appear to be widespread among bacteria and may explain the cross reactions reported between trichinella and certain diseases of bacterial origin.

STANDARDIZATION

The standardization of trichinella extracts poses some difficulties not encountered with other allergens. This is mainly due to the extreme dilu-

Fig. 31. As in Figure 30 but with the extract on the right heated to 100°C. for thirty minutes, appearance after about two weeks.

Fig. 32. As in Figure 31 but with the extract on the right autoclaved for thirty minutes.

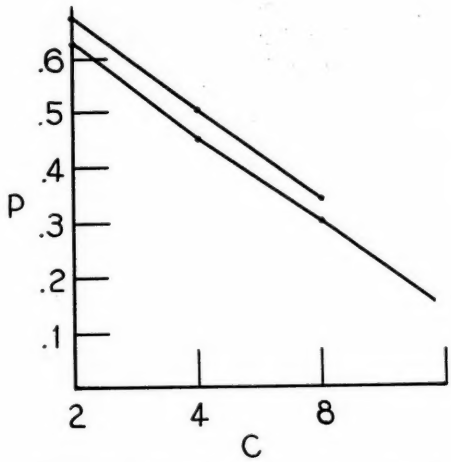


Fig. 33. Penetration rates (P) of dilutions (C) of trichinella extract diffusing into serum agar 1:12. Readings at 42 hours, upper, and 185 hours, lower graph.

tion of the material usually required to be assayed, since it is used at a concentration of 1:4000 or less for skin testing. This attenuation and its further dilution necessary to establish the graph are subject to rapid loss of activity during the tests, apparently primarily due to depletion of the small reservoir of antigen contained.

TABLE I. COMPARISON OF TRICHINELLA EXTRACTS DIFFUSING INTO SERUM AGAR 1:12. D, DISTANCE OF PENETRATION; P, ITS RATE.

Dilutions	Ext. 391				Ext. 392	
	42 hours		185 hours		42 hours	
	D	P	D	P	D	P
1:200	4.4 4.3	.670	8.4 8.6	.625	4.4 4.3	.670
1:400	3.3 3.2	.502	6.2 6.0	.450	3.3 3.3	.509
1:800	2.2 2.2	.340	4.0 4.2	.302	2.2 2.2	.340
1:1600	+ +		1.8 2.0	.140	+ +	
1:3200			+ +			

When stock extracts of high concentration are available, standardization of trichinella extract presents no unusual difficulties. For example, it was required to compare a newly prepared extract with a preceding extract about two years old, both at a dilution of 1:200. A series of Oudin tubes were prepared in the usual way.[31] Into each was placed 0.75 ml of rabbit antitrichinella serum, 1:6, combined with an equal volume of 0.6 per cent melted agar. After chilling in the refrigerator the serum-agar was overlaid, in duplicate, with a series of two-fold dilutions of both extracts.

After forty-two hours in the refrigerator the distances of penetration of the major band were measured. These are recorded in Table I under D. The readings of both turned out to be practically the same, showing that the potencies of the two extracts, based on the major antigen, were identical.

The two extracts were also compared with each other in the Ouchterlony plates at concentration 1:200, diffusing against their homologous antiserum undiluted. The precipitation pattern obtained was that of complete identity, similar to those shown in Figure 2 and 30, thus establishing the identity of the two extracts.

It will be noticed in Table I that the greatest dilution to give a measurable band at forty-two hours was 1:800. The next higher dilution, 1:1600, showed the precipitation band formed vertically on the interphase boundary and not measurable, indicated in the table by the + signs. At 185 hours the precipitation band of this dilution had passed the boundary and was just measurable as shown in the table. At this time the precipitation band in the 1:3200 dilution was on the meniscus of the interphase boundary and here it stayed; a later reading at 354 hours showed that it had not moved. This, then, is the equivalence dilution; 1:3200 of the antigen is equivalent to 1:12 dilution of the serum. At further dilution the direction of the diffusion is in reverse. In such a system the range of available dilutions is thus self limiting.

TABLE II. COMPARISON OF TRICHINELLA EXTRACTS DIFFUSING INTO SERUM AGAR 1:50. D, DISTANCE OF PENETRATION; P, ITS RATE.

Dilutions	Ext. 391		Ext. 392	
	D	P	D	P
1:2000	4.4 4.3	.520	4.3 4.4	.520
1:4000	3.1 3.0	.365	2.9 3.0	.353
1:6000	2.5 2.5	.298	2.2 2.4	.278
1:8000	1.7 1.9	.215	1.8 1.9	.221
1:10,000	1.2 1.3	.149	1.1 1.3	.143
1:12,500	0.8 0.9	.101	0.5 0.9	.084

The penetration rates of the advancing band in the higher concentrations were calculated by dividing the distances of penetration by the square root of the time.[31] These values are shown under P in Table I. A later reading was taken at 185 hours as shown in the table. The values of P for this are distinctly lower than those of the earlier reading, indicating that the penetration rate is slowing down. However, if these rates are plotted against the logarithm of the initial concentration (Fig. 33), they are seen to fall in lines which are approximately straight and parallel, showing that the deceleration affects the different dilutions about the same. Hence, the method can be used for standardization if a standard antigen is used for reference.

The problem of the weaker antigen dilutions, such as are used in the diagnosis of trichinosis, is more difficult. Theoretically, the point of equivalence can be placed anywhere at will by diluting the serum. Unfortunately, the density of the precipitates is determined by the concentration of the antiserum, so its dilution ultimately reaches a point where no visible precipitate is formed. With this serum the extinction point was found a little over 1:30 dilution. At this dilution, visible but faint precipitation bands could be measured with antigen dilutions down to 1:17,500, but when these measurements were plotted against the logarithm of the antigen concentrations they were too irregularly disposed to be reliable.

With a serum dilution of 1:25 the same two extracts shown in Table I were again put to the test at greater dilution. The results are shown in Table II. Again we find the extracts of equal potency, and the dilutions used cover at least most of those used for diagnostic material.

When these two extracts, at a dilution of 1:4000, were diffused against their homologous antiserum in the Ouchterlony plates, patterns of identity were formed; however, only the two bands representing the inner and outer groups were formed, instead of the usual ten obtained with more

TABLE III. FOUR SUCCESIVE READINGS OF THE DIFFUSION OF TRICHINELLA EXTRACT INTO SERUM AGAR 1:50. D, DISTANCE OF PENETRATION; P, ITS RATE.

Dilutions	25 hours		121 hours		192 hours		259 hours	
	D	P	D	P	D	P	D	P
1:4000	2.7 2.5	.520	5.0 5.0	.455	5.8 6.0	.425	6.4 6.6	.405
1:6000	2.0 2.0	.400	3.7 3.8	.341	4.3 4.4	.314	4.7 4.7	.292
1:8000	1.9 1.7	.360	3.2 3.0	.282	3.3 3.2	.235	3.4 3.6	.218
1:10,000	1.6 1.6	.320	2.5 2.5	.227	2.5 2.3	.173	2.5 2.3	.148

concentrated extracts, thus furnishing only incomplete information about their antigenic structure.

A much greater defect in the system is the tendency for the penetration rates to slow down, which we saw in the higher concentrations. This deceleration is greatly increased at lower concentrations, and in serial dilutions it increases at a surprisingly high ratio with the further dilution, making it impossible to establish a standard graph for the serum.

This is seen in Table III, which shows four successive readings of the distance of penetration at low concentrations and their calculated penetration rates. It will be noticed that there is a falling off in the value of P in all dilutions, which is much more rapid in the 1:10,000 than in the 1:4000 dilution. In the 1:10,000 dilution the readings of D show that penetration has stopped at 121 hours, and in the 1:8000 it has almost stopped at 192 hours. Obviously, values assigned to P under these circumstances are meaningless. It is thus impossible to establish a standard graph with antigen dilutions of this order of magnitude.

On the other hand, if a standard antigen is carried along with the unknown and the two happen to be the same or nearly so, standardization can be accomplished since both are affected alike or approximately so by the deceleration. But if one solution should be significantly different from the other, no comparison can be made except to point out which is the stronger.

SUMMARY

By means of the gel diffusion techniques of Oudin and Ouchterlony, it has been shown that extract of *Trichinella spiralis* gives ten precipitation bands with its homologous rabbit antiserum prepared by injection, indicating the presence of at least ten precipitating antigens. The pattern of their formation consists of an inner group (nearest the antibody source) of five bands, an outer group of four and a more distal dissociated band. One of the outer group is heavier than the rest, whitish and opaque in appearance and is believed to represent the major antigen.

Heating trichinella extract to 58°C for one hour was found to have no effect upon either its potency or precipitation pattern. Heating to 100°C leaves the antigens of the inner group unaffected, but completely destroys the major antigen and more or less weakens two of the others of the outer group. Autoclaving for one hour destroys all antigens except one of the outer group. Acidulating trichinella extract to pH 4 precipitates some of the material but has no effect on the potency or precipitation pattern.

Digestion of the extract with trypsin destroys all antigens of the inner group but has no effect upon those of the outer. Digestion with pepsin destroys all antigens except one of the outer group, the same one that survives autoclaving.

The sera from six active or convalescent human cases of trichinosis were found to give precipitation patterns with trichinella extract. In all cases the titers of those antisera were relatively very low. However, the precipitation bands could be identified with those of the outer group of the rabbit antiserum. Both normal human serum and pooled gamma globulin were found to be free of demonstrable trichinella antibodies.

Trichinella extract was found to give a slight cross reaction with *Dipylidium caninum* (Cestoda) but none at all with *Ascaris lumbricoides* nor *Toxascaris canis* (Nematoda). On the other hand, the two latter gave patterns of almost complete identity with each other.

Trichinella extracts in concentrated form can be standardized in the same way as pollen extracts, provided the antigen is used as the standard of reference, but this is not true of the diluted diagnostic extracts.

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Submitted October 21, 1955

SKIN TESTS WITH BACTERIAL ANTIGENS IN RHEUMATOID ARTHRITIS

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THE idea that infection is important in rheumatoid arthritis is persistent. The advent of ACTH and cortisone removed the spotlight from the controversial role of infection in rheumatoid arthritis. The total evidence is persuasive that occasional cases are greatly benefited by vaccines[10,16,22,23,27] and by effective treatment of foci of infection.[9,14,16,17] It has been easy to point out that available evidence does not prove that infection plays an important etiologic role. On the other hand, there has been no real effort to disprove claims of an important role of infection in individual cases.

In 1949, the results of an investigation in this laboratory, in which nearly 4,000 skin tests were done with thirty-four polysaccharide and nucleoprotein fractions of fourteen different bacteria on an unselected series of allergy patients, were reported.[15] The spectrum of positive reactions obtained in this investigation was so broad that a similar study of the skin reactions of a series of rheumatoid arthritis patients seemed worth while, especially since the incidence of skin reactions to hemolytic streptococci has been emphasized so much.[4,6-8,13,22,23,27]

Three sets of tests were performed. In the first set, several mixtures of bacterial vaccines and of nonbacterial antigens were used; in the second, mixtures of polysaccharide and nucleoprotein fractions of certain microorganisms; and in the third, mixtures of seventy-two-hour-old broth culture filtrates of microorganisms. The bacterial and nonbacterial antigens used for the skin tests were selected arbitrarily from materials available in the allergy laboratory.

The staphylococcus toxoid, and the brucella, typhoid and Cecil's strain of arthrotropic vaccines were commercial preparations. The staphylococcus, streptococcus, micrococcus, and *E. coli* vaccines were stock mixtures made in this laboratory. The stock respiratory vaccine was a mixture of killed organisms cultured from many asthma patients.

The number of patients tested with each antigen and the number of positive and negative immediate and delayed reactions obtained with each antigen are given in Tables I, II and III. The few discrepancies in the tables between the number of recorded immediate and delayed reactions to the individual antigens are due to failure to record some of those reactions when the tests were done.

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TABLE I. RESULTS OF SKIN TESTS WITH VACCINES AND ALLERGENS†

Vaccine or allergen	Immediate reactions*						24-hr. delayed reaction*					
	No. patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests	No. patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests
Staphylococcus mixture	162	118	40	4	0	44	159	103	32	23	1	56
Streptococcus mixture	158	128	27	3	0	30	158	133	20	5	0	25
Brucella vaccine	159	143	14	2	0	16	159	137	11	7	4	22
Micrococcus mixture	159	147	12	0	0	12	155	110	29	15	1	45
Escherichia coli	158	134	22	2	0	24	157	59	39	40	19	98
Typhoid vaccine	158	126	25	7	0	32	153	43	28	52	30	110
Stock resp. vaccine	157	110	43	4	0	47	157	94	43	19	1	63
Stock arthritis antigen†	162	23	70	68	1	139	157	32	43	47	35	125
Cecil's vaccine†	146	100	44	2	0	46	156	71	43	34	8	85
Staphylococcus toxoid	154	17	75	61	1	137	155	35	27	50	43	120
Dust mixture	146	44	69	33	0	102	151	97	33	16	5	54
Stock fungus mixture	144	85	43	16	0	59	151	70	48	31	2	81
Horse dander	151	78	59	14	0	73	151	129	19	2	1	22
Orris root	150	80	55	15	0	70	151	123	15	12	1	28
Totals	2164	1333	598	231	2	831	2170	1236	430	353	151	934

The discrepancies between the figures in the two columns "No. tested and observed" are due to failure to record some of the reactions.
† See text.

*The criteria for grading these skin reactions were:
Negative: No reaction.
Immediate reactions:
Weak: Faint pseudopodia; slight enlargement of mechanical wheal; 2-3 mm. flare.
Moderate: Definite pseudopodia; wheal roughly 1 cm. in diameter; flare roughly 1 cm.
Strong: Wheal 1.5 cm. or more, with large pseudopodia; flare 1.5 cm. or more.
Twenty-four hour delayed reactions:
Weak: 1.0-1.5 cm. palpable red area.
Moderate: Indurated red area, 1.5-2.0 cm. in diameter.
Strong: Indurated red area over 2.0 cm. in diameter.

TABLE II. RESULTS OF SKIN TESTS WITH MIXED POLYSACCHARIDE AND NUCLEOPROTEIN FRACTIONS† OF 12 BACTERIAL SPECIES

Bacterial species	Immediate reactions*						24-hr. delayed reactions*					
	No. patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests	No. patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests
Staphlococcus pyogenes	104	73	25	5	1	31	103	71	23	8	1	32
Neisseria catarrhalis	104	91	13	0	0	13	103	77	23	3	0	26
Escherichia coli	85	76	8	1	0	9	85	59	18	8	0	26
Streptococcus fecalis	65	53	9	3	0	12	64	47	13	3	1	17
B. hemo. streptococcus	77	63	11	3	0	14	76	52	15	7	2	24
Streptococcus pyogenes viridans	88	78	9	1	0	10	88	81	5	2	0	7
Pseudomonas aeruginosa	89	73	15	1	0	16	88	73	14	1	0	15
Klebsiella pneumoniae	73	65	7	1	0	8	72	63	6	3	0	9
Vibrio subtilis	60	58	2	0	0	2	59	57	1	1	0	2
Aerobacter aerogenes	58	53	5	0	0	5	57	48	5	4	0	9
Proteus vulgaris	82	74	7	1	0	8	81	62	14	5	0	19
Diplococcus pneumoniae	32	30	2	0	0	2	31	28	3	0	0	3
Totals	917	787	113	16	1	130	907	718	140	45	4	189

The discrepancies between the figures in the two columns "No tested and observed" are due to failure to record some of the reactions.
*See footnote to Table I.
†See reference 13.
†See reference 15.

TABLE III. RESULTS OF SKIN TESTS WITH MIXTURES OF FILTRATES OF 72-HOUR BROTH CULTURES

Bacterial species	Immediate reactions*						24-hr. delayed reactions*					
	No patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests	No. patients tested and observed	Neg.	Weakly pos.	Mod. react.	Strong react.	Pos. tests
Staphlococcus pyogenes	98	83	12	3	0	15	96	57	27	10	2	39
Neisseria catarrhalis	98	84	12	2	0	14	97	70	25	2	0	27
Escherichia coli	98	81	16	1	0	17	97	58	21	17	1	39
Streptococcus fecalis	95	81	12	2	0	14	93	79	15	0	0	15
B. hemo. streptococcus	94	80	14	0	0	14	93	80	10	3	0	13
Streptococcus pyogenes viridans	94	85	8	1	0	9	94	82	10	1	1	12
Pseudomonas aeruginosa	94	77	15	2	0	17	93	57	25	10	1	36
Vibrio subtilis	90	80	10	0	0	10	89	71	13	5	0	18
Aerobacter aerogenes	97	83	14	0	0	14	96	59	29	8	0	37
Proteus vulgaris	89	70	18	1	0	19	87	36	37	12	2	51
H. pertussis	88	73	15	0	0	15	86	38	28	19	1	48
Totals	1035	877	146	12	0	158	1021	686	240	87	8	335

The discrepancies between the figures in the two columns "No. tested and observed" are due to failure to record some of the reactions.
*See footnote to Table I.

Table I summarizes the results of the (2,164) skin tests with the vaccines and with the allergens. Approximately 38 per cent of these tests resulted in a positive reaction of the immediate type, and 45 per cent of them in the delayed type. Whereas the 353 moderate and 151 strongly positive delayed reactions were more impressive than the 231 moderate and two strongly positive immediate reactions, the significance of these differences, and those in the other tables, is obscure.[15,25,26] The stock streptococcal and staphyloccal vaccines were obtained from asthma and not arthritic patients. Note that there was no preponderance of reactions to Cecil's strain of arthrotropic vaccine. The numerous reactions to the stock arthritis antigen probably reflect its polyvalence.

Table II summarizes the results of the (917) skin tests with mixtures of crude polysaccharide and nucleoprotein fractions of several strains of the bacterial species listed. The hemolytic streptococcus and the pneumococcus mixtures are not comprehensive, since they contain fractions from only a few of the many sub-types of each of these species. The incidence of immediate and delayed reactions of all intensities was less than in Table I and there was no real preponderance of reactions to any one antigen.

Table III contains a summary of the (1,035) skin reactions to mixtures of filtrates of seventy-two-hour broth cultures of several strains of the species of organisms listed. The incidence of reactions was between those shown in Tables I and II. There was no preponderance of reactions to any one species of organism.

TREATMENT WITH STOCK ARTHRITIS ANTIGEN

Sixty-four patients were treated with injections of an arbitrary mixture of the antigens which had elicited so many positive skin reactions. All of them were given the same mixture, designated as "stock arthritis antigen," which is a "soup" containing a mixture of the antigens listed in Table I.

Injections of the antigen were given twice a week initially, starting with 0.05 cc of a 1:10,000 dilution. Ten increments of 0.05 cc were given from each ten-fold concentration until a dose of 0.3 cc of the concentrated antigen was reached. This was given once a week as a maintenance dose.

The sixty-four patients were treated with the antigen mixture for from one-and-one-half to two years. Little or no effect was noticed in fifty-six of the cases. In five patients the mixture was thought to be definitely helpful. In three other patients marked and prolonged remissions were attributed to the antigen.

DISCUSSION

The etiology of rheumatoid arthritis remains obscure. Lack of proof should not damn the idea that infection plays an important role in some

cases, since evidence in support of it keeps cropping up. Until the etiology is established, any suggestive evidence should be entertained until disproved. The emphasis on streptococci[1,4,5,11,19,20,22,23,27] in this connection has been diluted by the results of the skin tests reported here. The claims of Crowe[10] for staphylococci, of Sabin,[21] Preston,[18] and Brown[3] for pleuropneumonia organisms, of Fishbaugh[12] for the colon bacillus, and of Bocking and Brien[2] for the experimental production of arthritis by Old Tuberculin and egg albumin, have further de-emphasized the role of streptococci in the development of rheumatoid arthritis. These and many other data offer the strong suggestion, that at least some rheumatoid arthritis cases are caused by a delayed-type of antigen-antibody reaction which may be initiated by a variety of antigens.

There was no evidence that those antigens which elicited even the strongest skin reactions were of etiologic significance in any of the cases tested. The skin reactions in the eight cases which seemed to benefit from the injections of the antigen mixture did not differ from those which were not benefited. A similar variety of reactions was obtained in this laboratory in a large number of nonarthritic patients.[15]

It is difficult to reconcile the high incidence of unequivocal therapeutic failures in these cases with the high incidence of good results reported by Cecil,[4] Crowe,[10] Small and Small,[22-24] Wainwright,[27] and others. This becomes particularly difficult when it is recalled that the antigen mixture contained a variety of staphylococcal and streptococcal antigens, including the commercial arthrotropic strains.

It seems obvious that these skin tests, with a variety of bacterial antigens, did not help in the identification of the cause of the arthritis in any of these cases.

It is equally obvious that a specific effect cannot be claimed for the unequivocal improvement which followed the use of the antigen mixture in eight (12.5 per cent) of the sixty-four cases. By the same token it cannot be proved that the improvement was *not* due to a specific effect.

SUMMARY

The results of over 4,000 skin tests with a wide variety of bacterial and other antigens in a series of patients with rheumatoid arthritis are reported. Of sixty-four patients that were treated with a mixture of these antigens, only eight showed unequivocal improvement.

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Submitted July 18, 1955.

AMERICAN ACADEMY OF NUTRITION

The American Academy of Nutrition will hold its annual convention at the Hotel Statler in Los Angeles, California, May 18 and 19, 1956. The theme of the meeting will be "Degenerative Diseases," and there will be both guest speakers and panel discussions.

PSYCHIC FACTORS IN ALLERGY AND THEIR TREATMENT

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EVER since the time of Hippocrates,[6] physicians have been influenced by his observations that emotional imbalance may precipitate or intensify the various types of allergic patterns to be found in asthma, eczema, rhinitis, hives, and similar syndromes. There is still opposition to the application of psychotherapy in the allergic states, not only because unconscious motivation in disease is difficult for the organically trained physician to accept, but also because the obscurantist forces of specialized psychiatric terminology have prevented the average physician from understanding the role of technically important psychic factors. There are two general problems to be solved: (1) for the patient: to determine if specific (antigenic) factors or nonspecific psychic factors produce or intensify the allergic state; (2) for the physician: to communicate to the practicing doctor—whether general physician, allergist or psychiatrist—how he may employ the knowledge of any of these immunologic and psychologic processes in the treatment of the patient.

THE PSYCHOSOMATIC TRIANGLE[3]

It is well for us in discussing psychologic factors to group together both conscious and unconscious psychic forces and visualize an allergic symptom as the hypotenuse of a right triangle. I have called this triangle the "psychosomatic triangle," for it applies to the cause and management of all illness. Let any symptoms, say hives, be represented by a straight line. Let this straight line be made the hypotenuse of a right triangle. The triangle will then consist of the hypotenuse representing the symptom and two sides. (In vectors, the hypotenuse can always be resolved by two other vectors, as illustrated in Figure 1). Let one of the sides, the vertical one, represent psychologic or emotional factors producing the hives. Let the other side, the base, represent the somatic or physiologic factors producing the hives. This is our basic diagram depicting a fundamental fact, that in all patients with hives both emotional and physiologic factors must be involved. The question which confronts us is, "What is the relative importance of these factors in any particular instance?"

When a child regularly gets hives after ingestion of eggs, fundamentally speaking, the somatic (immunologic) factors are primarily involved, with emotional factors only secondarily involved (e.g., affecting, possibly, the permeability of the intestinal tract as well as the tonus of the skin vessels). In this case, primarily immunologic in nature, the psychosomatic triangle should be drawn differently to illustrate the case, as in Figure 2. The base of the triangle should be made long, compared with the vertical

side representing the emotional processes, to illustrate the relative importance of the forces at play. The emotional side (vector) never disappears entirely. On the other hand, there are certain cases of hives in which, as far as all available immunologic techniques have shown, the

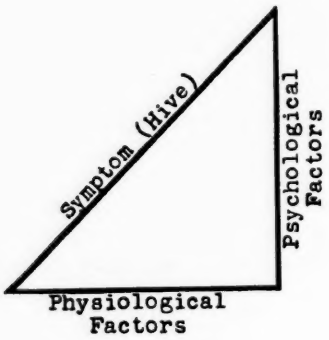

Fig. 1.

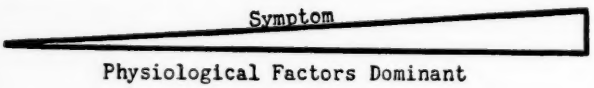

Fig. 2.

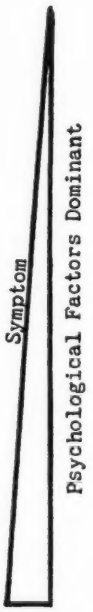

Fig. 3.

unknown theoretical or possible immunologic factors are far outweighed by what is actually known of the emotional factors in connection with both unconscious conflicts and conscious, realistic situations. In this case (Fig. 3), the vertical leg of the triangle is drawn larger to illustrate the importance of psychomotive forces. For example, in dermographism, there is no question that emotional factors plus mechanical tension on the skin produce the hive. Similarly, there are innumerable cases reported in the literature in which the hives immediately follow episodes of anxiety or are incidental to conflict situations. These hives persist for long periods in individuals who show no immunologic allergic reaction which can be demonstrated by our present methods.

If we include the basic science of psychodynamics as part of the discipline of the allergist, the practice of allergy will be released from the restrictions imposed by the specificity of immunologic reactions. Included within the specialty of allergy will then be a conscious attempt to diagnose and treat disturbances of neurovascular physiology not primarily de-

pendent upon immunologic mechanisms. The field of the allergist defined in this broader sense need not then depend upon variations in immunologic specificity alone, but is expanded to include altered reactivity by other processes. It is the application of psychodynamics to these processes which is now required for understanding and treating these clinical entities.

SPECIFIC FACTORS

French and Alexander,[5] who treated by psychoanalytic methods twenty-seven cases of bronchial asthma, found various personality types. However, they felt that a constant finding was a basic fear of separation from the mother or the mother figure. It was suggested that asthma may be the equivalent of a cry of rage or anxiety which has been inhibited or replaced. In some cases, over-protection by the parents and disapproval by them of psychosexual maturity was believed to be an important cause. The psychologic defenses employed by the person with asthma do not seem to be specific for the allergies, for confession, conformance, ingratiation, and utilization of the illnesses all fit in with the patterns of neuroses found in people who are not asthmatic. Many attempts have been made in recent years to classify the allergic dermatoses on the bases of specific patterns. In the experience of the writer,[4] the most important factors have been the unorganized and unrecognized rage of the allergic child toward the parent usually of the same sex. To identify with this parent means normal psychosexual growth. But to identify with someone against whom there is a volcanic inner rage constantly interferes with normal identification processes. This is striving for the impossible without some neurotic utilization of the basic allergic illness. This inner rage is turned by the patient outwardly against himself and leads to a prolongation of the allergic eczema. We all have seen the remarkable elimination of allergic dermatoses when the emotional situation is changed. In asthma the parentectomy of Peshkin[7] is perhaps an extreme example, but does not provide the basic psychodynamic mechanism. We know little about the intensity of each of the processes and have much to learn by co-ordinated study of allergic and psychic forces.

We must never forget that a chronically ill individual is anxious, and the treatment of this anxiety is a necessary part of the therapy of the allergic patient no matter how well controlled the immunologic mechanisms may be. This anxiety may be expressed outwardly to the physician by the dominant expression of anxiety, depression, grief, hostility, phobia, and euphoria, among others. The management of these symptoms is discussed elsewhere in detail.[2]

In view of the difficulties of giving explicit and specific formulations which satisfy statistical reasoning and the combined experience of both allergist and psychiatrist in allergy, I shall attempt to systematize here psychodynamic forces which might be of significance, by taking up the general nature of the psychotherapeutic possibilities of allergic patients.

Generally speaking, psychotherapeutic processes may be divided into two types:

I. Automatic Psychotherapy.

II. Purposeful or Planned Psychotherapy.
   (a) Reassurance (pharmacologic and supportive).
   (b) Educative with insight.
   (c) Reconstructive psychotherapy with insight.

What do all of the foregoing groupings mean to the practicing allergist?

NATURE OF THERAPY IN ALLERGY

I. Automatic Psychotherapy

Automatic psychotherapy begins when the patient decides to seek the advice of his physician for symptoms, whether hay fever, asthma, or any other symptoms. He is seeking to establish a relationship with another person, a physician, trained not only in the skills of modern medicine but carrying with him the tradition of centuries of medical learning and interest. As the patient enters the doctor's office, this relationship continues and is developed through the interview with the nurse. The doctor's assistant is usually a woman who, together with the physician, plays the role of automatic supporting figures, psychodynamically speaking, parental figures, who will listen sympathetically to the complaints of the patient. The furniture in the consulting room, the credentials framed on the wall, pictures of famous physicians of the past and of the present, equipment in the examining room, all reinforce the automatic psychologic processes of therapy that are taking place.

As the doctor takes the history, there is demonstrated to the patient that the physician is not only interested in the *things* to which he is sensitive, but also, without explicitly stating so, in the *people* to whom he might be sensitive. All the loves, the hates, and the anxieties of the patient are directly or indirectly touched upon or even avoided during the taking of the history. The patient realizes that this may be just the beginning of a new and important personal relationship which will help him solve many of his problems, not only on a physical level, but also on an emotional level without stating this explicitly at the time of taking the history. Bear in mind the psychotherapeutic value of a careful physical examination, blood count, nasal smear, skin tests, and other laboratory devices which, slowly but inevitably, give the patient an understanding of the nature of his symptoms. True it is that these are physical procedures, but there is an implicit psychologic vector which cannot and should not be underestimated.

Finally comes the decision of the physician: "I recommend that . . ." At last, the person with whom the patient has established an important new relationship or re-established an old one gives his conclusions and summarizes what he thinks therapy should be. The patient's symptoms, no

matter how trivial or how serious, have now become a part of the doctor's life. This is an important process which led the patient in the first place to share his needs with the doctor and with his other assistants if present. The writing of a prescription or the injection of a therapeutic solution may be a physical process, but the symbolic meaning of these, whether a potent drug or a harmless placebo, all carry with them the search of one group of men, the physicians through the ages, for techniques to heal the sick.

II. Planned or Purposeful Psychotherapy

(a) Reassurance.—We have thus far discussed only the automatic psychotherapy which the patient encounters even though the physician is an organicist who does not "believe in psychiatry." Perhaps the foregoing discussion will enable the strictly organically minded physician to accept the point of view that he is inevitably involved in a psychotherapeutic relationship with the patient, no matter how physical his procedures. Leaving this automatic type of psychotherapy, I shall now try to show how planned or purposeful psychotherapy may be employed by the allergist in the great majority of cases leaving reconstructive psychotherapy, usually psychoanalysis, for only a minor fraction of his patients. It should be borne in mind at this point that this discussion does not include psychotics, borderline psychotics or near psychotic personality structures. This group requires much more complicated management than is usually available in the allergist's office. However, a certain number of these patients are aways present in the population of any physician's practice, and it is wise to know that the automatic psychotherapy procedures are even more potently operating with them, perhaps, than with the nonpsychotic population.

Let us now take up a very safe and satisfactory type of planned or purposeful therapy, e.g., reassurance. In this category of planned psychotherapy is the reassurance given to the patient by the physician who will tell him that his difficulty in breathing is only asthma, that there is little or no danger of death, that with the administration of antiserum the physician is fully aware of the dangers of an anaphylactic reaction, that he understands the nature of the patient's problems, that the allergies are not a disease but a condition, that the hives are in all likelihood a transitory phenomenon—all are supportive psychotherapy. In addition, suggesting a vacation, new occupational interests, the establishment of new friends and interests outside of self—all may be utilized by any physician and applied to a major fraction of his patients. There is no danger whatsoever in utilizing supportive therapy of this type.

I have previously considered the pharmacologic aspects of this type of psychotherapy as *psychodynamic pharmacology.* In the treatment of the asthmatic patient, for example, recognition that ephedrine and epinephrine may increase the anxiety of the anxious patient and lead to a state

of "epinephrine fastness," the use of chloral hydrate to reduce anxiety, the employment of oxygen even though no cyanosis is present, the utilization of cortisone not only as an anti-inflammatory drug but also to induce euphoria, the recognition that amphetamine may aid the eczematous patient to emerge from a depressed state, the conscious utilization by the physician of the sedative effect of the antihistamine to ameliorate the anxiety of hives, all combine the best type of medical treatment because both the physical and the psychologic aspects of the patient's difficulties are being simultaneously treated by the drugs employed.

Not only does every physician, whether psychiatric specialist or not, have the right to use this type of therapy, but it is his Hippocratic duty to do so within the limits of his knowledge.

(b) Educative with Insight.—The second type of planned psychotherapy depends to a greater extent on the personality of the physician, his medical education, and his interest in psychotherapy. All physicians have had enough training to become appropriately active in educative psychotherapy, usually with the development of insight on the part of the patient. In this type of psychotherapy the physician sympathetically explores in more detail the personal and family relationships of the patient, his work relationships, and his position in the community. The nature of his difficulties on a conscious level are brought out and problems of adjustment leading toward better adaptation may be indicated or planned. Reading, such as *Emotional Problems of Living* by English and Pearson, is suggested, and the patient's childhood is discussed in terms of his present adult difficulties. In the case of the allergic child, more emphasis is placed on the parent-child relationship, and the problems connected with the establishment of a harmonious home are dwelt upon. Helpful are books such as Dorothy Baruch's *One Little Boy*, and other works. As I have mentioned elsewhere, I do not believe, however, in the theory of maternal rejection as the basic psychologic vector in allergy.[1]

Up to this point we have covered approximately 90 to 95 per cent of the average allergist's office population. It is the responsibility and the duty of the allergist, depending upon his personality and his interest, to understand and to implement as much of the foregoing types of psychotherapy as he can.

(c) Reconstructive with Insight.—A maximum of 5 per cent of the allergist's patient population is suited for reconstructive psychotherapy with insight. This usually means a psychoanalysis of 400 hours or more. Unfortunately, not only must the patient have the time and money to undertake this type of therapy, but he must also have sufficient ego strength to utilize the revelation of his unconscious. Reconstructive therapy should be performed only by those trained in this procedure. Although

5 per cent of the allergist's patient population may be benefited by this type of therapy, fewer than 5 per cent can have this type of therapy made available to them. Wohlberg[8] summarizes the question by stating that reconstructive therapy is indicated for those whose problems are initiated by severe distortions of parental relations which have produced retardation in maturity. Difficulties in which maturation is the chief defense of the patient may lead to the best therapeutic response.

SUMMARY

The psychotherapeutic potentialities practiced in ambulatory medicine are divided into two main types:

I. Automatic Psychotherapy

II. Purposeful or Planned Psychotherapy

The large majority of patients seen by the allergist can usually be treated by the allergist himself by all of the foregoing techniques except reconstructive psychotherapy, unless he is specially trained in this technique.

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Submitted October 19, 1955

VENEZUELAN SOCIETY OF ALLERGOLOGY

On February 1, 1956, in Caracas, Venezuela, the Venezuelan Society of Allergology was founded, and the following officers were elected:

President	Dr. A. Pérez Lozano
Vice President	Dr. Marcel Granier
Secretary	Dr. Otto Lima Gómez
Treasurer	Dr. Raúl Rodriguez Gragirena
Librarian	Dr. Jacinto Convit
Voting Members	Dr. Tobias Lasser
	Dr. Espiritu Santos Mendoza

EVALUATION OF ANTI-ASTHMATIC MEDICATION

A Critique

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DANIEL M. KRAUS, M.D.
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DESPITE all attempts at the evaluation of a drug by pharmacologic and toxicologic testing on animals, the ultimate value of a particular medication is determined by administration to humans under ordinary living conditions, a procedure termed "field trial." Field trial is especially important in assessing the value of anti-asthmatic medication, because the disease in many individuals is compatible with ordinary activity. The usual field trial of an anti-asthmatic drug utilizes ambulatory patients obtained from clinic and private practice and usually grouped together. Frequently in this type of clinical evaluation, early therapeutic successes reported by one or more investigators are not confirmed by later workers.

Bancroft[1] pointed out that one source of diversity of opinion concerning the value of an anti-asthmatic drug arises from failure to employ control groups. The necessity for the use of control groups is based upon the unreliability of subjective symptomatology, variation in environmental factors and pollen exposures, and other unknown etiologic factors. In setting up control groups, she urged that selection of cases be weighted as far as age, sex, race and severity of the disease. These comments of Bancroft crystallized our own thinking concerning participation in drug evaluation studies. A statistically valid field trial appeared to us to be nearly impossible in the ordinary clinic or private practice.

When we were requested recently to evaluate aminophylline spansules,® in the treatment of asthma, the above-stated reservations were given the pharmaceutical manufacturer. Nevertheless, we undertook the study. Our experience was illuminating, for it showed that evaluation in an institution such as the Jewish National Home for Asthmatic Children demonstrated advantages over evaluation in clinic or private practice. This paper will therefore discuss only the broad concepts involved in the study without regard to the efficacy of the drug used in the study.

SELECTION OF CONTROL GROUPS IN ASTHMA

The ideal protocol for therapeutic evaluation of an anti-asthmatic medication should employ not only controls but also controls which are paired—one member of the pair receiving the medication and the other member receiving a similarly appearing but inactive substance. The conditions necessary for selection of the paired controls must include: (1) the same

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degree of respiratory disability, inferring the same degree of pathophysiologic diseases; and (2) the same clinically significant etiologic factors, including allergenic materials (e.g., pollens, foods, animal danders), infectious factors, irritant dusts and smokes, psychogenic factors, and climatic factors such as temperature and humidity.

The above conditions cannot be fulfilled. Even if the individuals were to be under twenty-four-hour observation for months to determine all possible etiologic factors, no pair of chronic asthmatic patients could conceivably be so evenly weighted as regards the above-mentioned factors to warrant the scientific term of "control." The classification of Brown and Halpin[2] attempts to simplify the matter so that each physician can assess asthma and can speak of the problem so that his colleague can interpret results. Yet, Halpin, in discussion of this paper, aptly comments on the lack of criteria for estimation of severity. He states, "What was severe to one man was considered moderate to another. . . ." These remarks lend further support to the concept that selection of control groups in asthma with regard to severity of disease is practically impossible. Thus, we are forced to accept the concept of using the individual himself as the control —the control in this instance being the baseline behavior over a period of time long enough to determine in that individual the clinically observed factors operating to produce asthmatic symptoms. Once this basal asthmatic state has been determined, the addition of a new drug to the therapeutic regime will allow a reasonable conclusion as to its therapeutic efficacy.

ACUTE VERSUS CHRONIC ASTHMA

Determination of baseline behavior with regard to symptoms of asthma implies constancy of these symptoms. In other words, chronic asthma must be the determining factor. The following case illustrates this point:

> K. D., age ten years, was admitted to the hospital of the Home from her cottage because of severe asthma. The drug to be tested was started. Symptoms of asthma subsided the next day and the child was discharged. The drug was administered on an out-patient basis for one week and then stopped. Asthma did not recur for six weeks.

It would have been easy to ascribe improvement to the medication used, but further observation showed that this child's asthma was of the acute type, that symptoms were not present between acute attacks and that this case should be deleted from the study.

Acute symptomatology may be described as asthma occurring with no residual objective or subjective symptoms between attacks. On the other hand, the chronic asthmatic patient is one in whom wheezing with or without dyspnea is present more or less constantly from day to day. Neither of the more recent classifications of asthma (Brown and Halpin,[2] Swine-

ford[3]) emphasize the distinction between acute and chronic asthma. Yet, in our experience at the Home, this distinction serves to clarify our thinking especially as to etiology and therapy. The case of acute, recurrent asthma is usually caused by a different group of factors than in the chronic case. Treatment must stress elimination of the respective etiologic factors and will therefore differ in each group. In order to make this important distinction, the patient must be carefully observed for a relatively long period of time, day and night. After determination, the cases of acute recurrent asthma can be eliminated from consideration in the group for drug evaluation. Faulty conclusions could result if relief of symptoms in this group were attributed to the drug rather than to a period of spontaneous remission. We believe that the chronic asthmatic cases constitute the only group in which a drug evaluation is possible. The pattern of disease in this group enables the observer to determine quickly the effect of a drug and the lack of effect of a placebo. Trials can be made over extended periods. If the drug under evaluation is effective, the pattern of the disease can be varied almost at the will of the observer.

Many patients with chronic asthma in our institution are emphysematous. There is some difference of opinion as to the role of emphysema in the production of chronic asthma. We usually cannot determine whether the chronic symptoms, wheezing, coughing, and dyspnea, are part of the picture of emphysema or of the asthma itself, with emphysema being only a result. For the purposes of drug evaluation, this is not a crucial point but is mentioned here to stress the fact that emphysematous patients ordinarily constitute a large majority of any drug test group.

Observation of chronic symptoms is difficult to make in private practice or in an outpatient clinic. We must then depend wholly on either the patient's or the parents' reports, and these are often unreliable. The Home permits objective observation over a twenty-four-hour period by each individual with whom the child has contact. Outpatients live in dormitory or cottage-like buildings with each group in charge of a houseparent. The houseparent lives and eats with the group. Within the younger age groups where nocturnal problems are frequent, there is an additional person on duty during the night for the sole purpose of accurate reporting of these occurrences to the medical director. Our patients attend public schools within walking distance of the Home. School teachers and school nurses are taught to recognize and report asthmatic symptoms. Thus, there is a full round-the-clock reporting of all asthmatic symptoms with which we are concerned in the evaluation of anti-asthmatic medication. Thus the determination of baseline level of asthmatic symptoms is carried out with greater facility and accuracy at the Home than in non-institutional settings. Nevertheless, the institutional setting has sufficient elements of normal living to enable us to call our evaluation of medication a "field trial" with some justification.

ENVIRONMENTAL FACTORS

Having established the principle of the basal asthmatic status as the control, therapeutic evaluation of the anti-asthmatic drug requires careful observation of any concomitant change in the clinically significant environmental factors. The main categories are allergenic and nonallergenic.

1. Allergenic factors comprise pollens, molds, house dust, animal danders and foods. Since our around-the-clock personal observations shall have uncovered any allergic reaction to the above, the clinical effect of introducing a new medication will have to take into account variations in exposures to any of these allergens. Suppose we were at the end of the weed pollen season when the new medication was given to one of the weed pollen asthma cases—certainly the improvement noted in this patient could not be attributed to the drug. The same line of reasoning would extend to unusual exposures to animal danders, house dust, and to the ingestion of certain clinically allergenic foods.

2. Nonallergenic factors would include physical exertion, the advent of cold, windy weather, smog, smaze, and the exposure to irritant dusts and smokes. All physicians have among their chronic asthmatic patients certain individuals, who, with the passage of a cold front through the geographical area, develop wheezing, cough and dyspnea. If, during the period of evaluation of a new drug, the patient were exposed to cold weather, accompanied by gusty winds, followed soon thereafter by temperate, balmy weather, the value of the medication in causing the rapid subsidence of asthmatic symptoms would be seriously questioned. Many additional examples of how these nonallergenic factors can affect the patient with chronic asthma could be added, but it is our purpose merely to restate the principles necessary for evaluation.

PSYCHOPHYSIOLOGIC FACTORS

The concept of emotional tensions affecting the pattern of somatic disease has gained acceptance in all fields of medical practice. Bronchial asthma represents one disease in which the medical literature recognizes the influence of psychogenic disturbance. Our present knowledge does not allow any conclusion as to the pathophysiologic mechanism involved, but clinical observations in private patients and especially in those in our Home attest to the importance of consideration of these factors in the etiology of the intractable asthmatic. It follows that evaluation of an anti-asthmatic drug must allow for variations in the emotional factors of the case under observation. We have seen tension aggravate and continue asthmatic symptoms, and we have seen relief of asthma by reduction of such tension. Obviously, resolution of these tensions coincident with the use of the new drug would yield invalid conclusions. In the private and clinic asthmatic patients, the full significance of these emotional tensions does not allow as complete an evaluation as compared to our asthmatically oriented personnel, professional and lay. As an example, we can cite an

adolescent girl developing severe asthmatic symptoms following understandable arguments with her adolescent boy friend. And when the latter is also a chronic asthmatic patient, frequently he also will be observed with moderate to severe asthmatic symptoms. Only where these particular emotional factors can be observed, can one properly assess the value of any medication used in chronic asthma. It should be stressed that therapeutically active drugs may not protect against asthma caused by tension. Drugs may be excellent bronchodilators but be ineffective when used prophylactically. Intimate twenty-four-hour knowledge of the patient avoids false conclusions, especially in the emotional field.

SUMMARY

We have attempted to outline and discuss some factors which are involved in the evaluation of anti-asthmatic medication. Superiority of institutional evaluation has been pointed out. The concept of the knowledge of the basal asthmatic state as an acceptable substitute for the establishment of perfectly weighted control groups has been presented. It is our feeling that adaption of the enumerated principles will result in more accurate evaluation of the efficacy of anti-asthmatic medication.

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Submitted April 22, 1955

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Dr. James A. Shannon, Director of the National Institutes of Health, Public Health Service, has announced the appointment of Dr. Dorland J. Davis as Associate Director of the National Institute of Allergy and Infectious Diseases. In this newly established post, Dr. Davis will be responsible for the planning, organization, and direction of the Institute's research program in Bethesda and its field station in Hamilton, Montana. Dr. Davis has been with the Public Health Service since 1939 and has served as Chief of the Laboratory of Infectious Diseases since 1954. He is active in the work of the World Health Organization.

The National Institute of Allergy and Infectious Diseases, formerly the National Microbiological Institute, last month announced a major addition in its research activities. Present plans call for long-term basic studies in the fields of allergy and immunology, with emphasis on the support of scientists in the nation's universities and medical schools through grants-in-aid.

IS POLLEN A CONTRIBUTING FACTOR IN THE SEASONAL INCIDENCE OF POLIOMYELITIS?

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MUCH concerning the etiology of poliomyelitis has been established, but the reason for the seasonal incidence remains a mystery. Epidemiologic surveys have shown that poliomyelitis is endemic in the southern United States, while it is epidemic in the north. In all areas of the country, with the exception of the South Atlantic and West South Central States, the poliomyelitis season starts in June and usually reaches a sharp peak in August and September. In the South Central and West Central States, however, poliomyelitis incidence begins one month earlier. The onset of cold weather in any part of the country causes a sharp drop in poliomyelitis incidence; the likelihood of contracting poliomyelitis after the first frost is considerably diminished. Warm weather or something that happens in warm weather contributes to the seasonal outbreaks of poliomyelitis.

The increased incidence during the summer months has been attributed to a number of factors: feces, flies, water, milk, mosquitoes, birds, vegetables, fruits, dogs, fish, and sewage, to name just a few. Yet none of these has been widely accepted as responsible for the seasonal incidence of poliomyelitis.

Crouch[2] attempted to correlate seasonal incidence with the allergic suspectibility of poliomyelitis patients; nineteen out of twenty-seven cases (73 per cent) had a personal or family history of allergy. Schwarz,[7] in his survey, found that in forty cases, 21.5 per cent were personally positive for some asthma; 17.5 per cent had a family history of allergy. Recently Holbert[4] has reported that of 100 patients with severe residuals of poliomyelitis, 62 per cent had one or more of the following allergies: asthma, hay fever, eczema, chronic stuffy nose, urticaria or migraine. Lubens[5] found in 300 cases of poliomyelitis that 150 had some manifestation of an allergic condition. Thirty-nine of these people with allergic responses had bulbar poliomyelitis.

The most common causative agents in allergy are the pollens of various weeds and grasses. Peak air concentrations of most of these allergens occur during the months of August and September. The seasonal incidence of poliomyelitis tends to occur with the peak pollen count in the various regions of the country. For the sake of brevity only two sections of the country are depicted, but the temporal association between poliomyelitis

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incidence and pollen count of various weeds and grasses holds for all other regions of the United States that have been charted.

Figure 1 presents the ragweed pollen counts and poliomyelitis incidence for four consecutive seasons in Monroe County, New York. There are

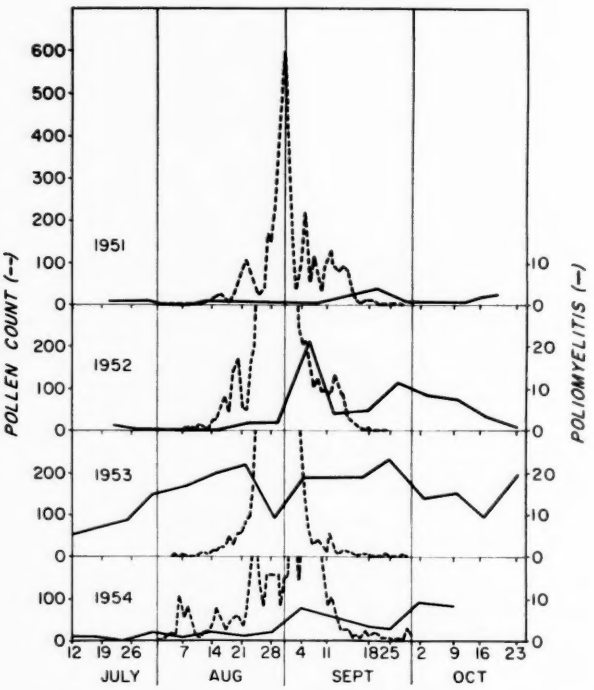

Fig. 1. Number of cases of poliomyelitis (solid lines) and ragweed pollen counts (dotted lines) in Monroe County, New York, July-October 1951-1954. Pollen counts furnished by Dr. Jerome Glaser of Rochester, New York. Poliomyelitis statistics furnished by the Rochester Health Bureau.

two sharp increases in the number of poliomyelitis cases; one in late August and early September, and the other in late September and early October. These data compiled for the years 1948-1954 permit the conclusion that the latter increase in poliomyelitis was always preceded by the peak ragweed pollen count twenty-three to thirty-four days earlier. This time interval was repeated year after year with great fidelity. There were marked variations in the heights of the peaks (number of cases) from year to year, but not in the length of the lag period from pollen count peak to poliomyelitis case peak.

The first peak in poliomyelitis cases (Fig. 1) took place prior to or

during the peak of pollen count. Unfortunately, although ragweed pollen is counted in Monroe County, information regarding the pollen maturation of other plants is lacking. From published data of the other areas, it is probable that a peak in the pollen count of grasses took place in

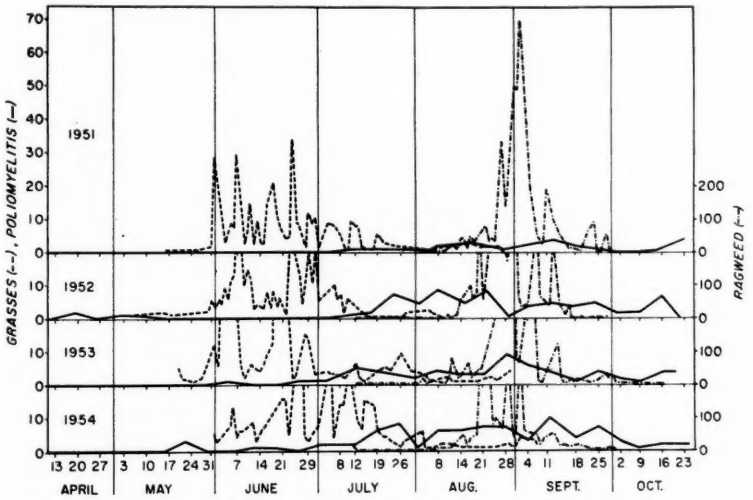

Fig. 2. Number of cases of poliomyelitis (solid lines) and pollen counts (dotted lines) in Washtenaw County, Michigan, April-October, 1951-1954. The peaks in pollen counts in June and July are grass pollens, those in August and September are ragweed. Pollen counts furnished by Dr. John M. Sheldon of Ann Arbor, Michigan. Poliomyelitis statistics furnished by the National Foundation for Infantile Paralysis.

June and July, thus possibly forming an allergenic stimulus preceding the earlier rise in numbers of cases in poliomyelitis when this occurred. For example, Figure 2 represents both grasses and ragweed pollen counts and poliomyelitis incidence for four consecutive years (1951-1954) in Washtenaw County, Michigan. These data show clearly that the pollination of grasses precedes the large early peaks in poliomyelitis cases.

An attempt was made to determine by means of skin test studies whether or not there might be any relationship between positive skin tests to pollen and the incidence of poliomyelitis. To this end a series of fifty unselected successive patients who had suffered from poliomyelitis were skin tested with ragweed and timothy pollen. Thirty-two, or 64 per cent, gave definitely positive reactions. The details of the skin tests are recorded in Table I. Of the fifty patients, there were ten who had a history of grass or weed pollinosis, and all of these gave positive skin tests to pollen. Eight of the patients had a father or mother with either

TABLE I. RESULTS OF SKIN TESTS WITH POLLEN IN 50 UNSELECTED PATIENTS WHO HAD SUFFERED FROM POLIOMYELITIS

Scratch or Interdermal	Total Patients 50	Spinal Paralytic	Abortive	Bulbar	Timothy	Timothy and Ragweed	Ragweed
Positive	32	23	5	4	7	17	8
Questionable	5	0	3	2	3	1	1
Negative	13	6	5	2			

grass or weed pollinosis. The personal and family histories of fourteen of the remaining patients were negative. From this it would appear that although the incidence of patients who had pollinosis and developed poliomyelitis is about the same as that of the general population (about 10 per cent), the incidence of positive skin tests is probably significantly higher than that of the general population.

In one series of sixty presumably normal adults, Rackemann and Simon[6] found an incidence of reactions to ragweed and timothy pollen of about 32 per cent. It was later shown, however, that 6.6 per cent of their cases had grass or weed pollinosis and therefore their series cannot be regarded as that of positive skin tests in normal individuals, but as skin tests in a series approximating random sampling of the general population. In another series of 150 presumably normal individuals carefully selected to rule out pollinosis and other allergies, Grow and Herman[3] reported positive skin tests to ragweed and timothy in about 18 per cent. Had their series been unselected as regards pollinosis, it is hardly likely that the percentage of positive reactions would have been more than doubled as a maximum. Also, in neither of these two series is it indicated whether or not, as is highly probable, some patients reacted to both ragweed and timothy. If this had been considered as only one reaction to pollen (as was the case in our series), the percentage of positive skin tests to pollen would have been somewhat reduced.

It would therefore appear from our small series that patients who have had poliomyelitis react to skin tests with pollen about twice as often as might be expected in a random sampling of the population.

Many conditions have been suspected of favoring a susceptibility to infection by poliomyelitis, e.g., pregnancy, tonsillectomy, adenoidectomy, immunization, injuries, fatigue, unusual exertion, cold and, as suggested here, allergy. All of these conditions are stresses which promote an increased release of histamine. Perhaps this release is part of the mechanism of infection with poliomyelitis. One of the major actions of histamine is to increase capillary permeability and lymph flow. In chimpanzees Bodian[1] noted that lymphoid tissue becomes infected before viremia. He suggests that lymphoid tissues and the structures which drain them are the primary pathways for viral infection. If the virus is present in the alimentary tract, the release of an agent which promotes capillary permeability and lymph flow may facilitate the entry of the virus into the body.

SUMMARY AND CONCLUSIONS

It is shown that the incidence of poliomyelitis parallels and shows peaks following the height of both the grass and weed pollen seasons. Evidence is also presented that patients who have had poliomyelitis react positively to skin testing with pollen about twice as often as might be expected in a random sampling of the general population. These factors suggest a possible relationship between poliomyelitis and pollinosis which may, however, be purely fortuitous. The hypothesis is, however, too attractive to be neglected.

ACKNOWLEDGMENT

The authors acknowledge the assistance of Victor DiStefano, Ph.D., and also wish to express their appreciation to Marilyn F. Smelzer, M.D., who did the skin tests with pollen.

Full appreciation is acknowledged for the co-operation of Jerome Glaser, M.D., Assistant Professor of Pediatrics, for his co-operation and review of this paper.

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Submitted February 20, 1956

ELEVENTH ANNUAL SCHERING AWARD COMPETITION OPENS

Dr. C. J. Szmal, chairman of the Schering Award Committee, has announced the subjects upon which papers may be written for competition for the eleventh annual Schering Award. The three subjects chosen for 1956 are: The Clinical Use of Adrenocortical Steroids in Collagen Diseases, Metabolic Aspects of the Aging Process, and New Applications of Antihistamines in Medicine and Surgery. A first prize of $500 and a second prize of $250 will be awarded for each of the three subjects. Literature and entry forms are being distributed in the medical schools, and students interested in participating should submit their entry forms to the Schering Award Committee, Bloomfield, New Jersey, before July 1, 1956. Manuscripts must be postmarked not later than September 30, 1956.

RECURRENT COMA CAUSED BY RESPIRATORY FAILURE

Report of a Case

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IT is now well recognized that carbon dioxide narcosis is occasionally induced by the administration of oxygen to hypoxic patients with chronic lung disease. [2,3,6,7] For this reason it is customary to introduce oxygen therapy cautiously to such patients. It is not so widely appreciated, however, that carbon dioxide narcosis can develop rapidly in persons with lung disease who have been on oxygen therapy for days or weeks and have previously tolerated oxygen well.

Carbon dioxide narcosis can develop in patients with disorders such as pulmonary emphysema, which cause chronic alveolar hypoventilation and consequently lead to chronic hypercapnia as well as hypoxia. With chronic hypercapnia the respiratory center becomes relatively insensitive to the arterial blood carbon dioxide tension and pH, and the stimulus to maintain ventilation must come from other sources. Hypoxia, acting through the arterial chemoreceptors, appears to be a major stimulus in some of these patients, as indicated by the great reduction in ventilation which occurs when hypoxia is relieved by oxygen. In other patients the major ventilatory drive is provided by stimuli other than blood gas tensions or pH. The nature of these additional stimuli is not completely understood, but they appear to be neurogenic and they evidently account for much of the ventilatory drive under normal conditions.[4]

The immediate effect of giving oxygen to an hypoxic, hypercapneic patient depends upon the nature of the stimuli which maintain his ventilation. If hypoxia is largely responsible, oxygen may cause so great a decrease in ventilation that carbon dioxide will accumulate rapidly to reach narcotic levels. If neurogenic stimuli are responsible, oxygen will have little immediate effect on ventilation, and carbon dioxide will not accumulate. However, neurogenic stimuli may fail unexpectedly in hypercapneic persons on oxygen therapy, and when they do fail, carbon dioxide narcosis develops quickly.

The reasons for failure of neurogenic stimuli are not at all clear. Oversedation[8] and the relief of pain in an exhausted or severely ill patient are factors in some cases. Once carbon dioxide narcosis has begun, extrachemical stimuli appear to be further depressed, and the narcosis deepens. Nevertheless, it is an interesting and surprising fact that these patients sometimes recover spontaneously from carbon dioxide narcosis. Occa-

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This work was supported by a research grant (Public Health Service H-1370) from the National Institutes of Health, Public Health Service.

sionally, hypercapneic, hypoxic patients have transient episodes of unconsciousness not induced by oxygen therapy. In such cases, hypoxia must contribute largely to the depression of the central nervous system.

Carbon dioxide narcosis which occurs unexpectedly in a middle-aged or elderly person is often mistaken for a cerebral vascular accident. The patient cannot be aroused and may not respond to painful stimuli. If oxygen is being given, cyanosis is usually not apparent. Respiration is usually shallow. The pupils are often constricted and may be unequal in size. The extremities are apt to be flaccid. Deep tendon reflexes are reduced or absent. Twitching, or even a convulsion, may occur. The cerebrospinal fluid pressure is usually elevated and can easily exceed 400 mm H_2O. The rise in cerebrospinal pressure apparently results from the cerebral vasodilatation caused by the high carbon dioxide content of arterial blood.

The treatment of narcosis is directed toward increasing alveolar ventilation. This comprises the use of bronchodilators, tracheal aspiration, antibiotics, steroid therapy, and the treatment of congestive failure if indicated. When narcosis is fully developed, the use of mechanical respirators such as the Drinker[1] or Seeler[5] types may be necessary. Norepinephrine is frequently useful to maintain blood pressure. Circulatory collapse is a common terminal event in these patients.

Once the acute episode has been controlled, attention should be turned to the correction of any reversible complications of the basic pulmonary disorder which may have appeared recently to set the stage for narcosis by further depressing pulmonary function. These reversible factors may affect the respiratory center, the lung itself, or the ability to move the chest wall. Oversedation, pulmonary infection and congestive heart failure are common offenders. Discouragement and reactive depression, with consequent loss of appetite, loss of weight, and ultimate loss of strength to move the chest adequately may be responsible for progressive pulmonary failure. Exhaustion from a prolonged attack of asthma in an elderly patient with emphysema may have the same effect.

It is the purpose of this paper to illustrate some of these features of carbon dioxide narcosis by reporting the case of a patient with asthma and emphysema who had recurrent attacks of narcosis, one of which required treatment with a respirator. In this patient with markedly reduced pulmonary function and hypercapnia, episodes of respiratory depression occurred both with and without oxygen therapy. Apparently both hypoxic and neurogenic ventilatory drives were inadequate.

CASE REPORT

E. E., a fifty-six-year-old unmarried librarian, had had recurrent asthma for thirty years and had gradually developed severe pulmonary emphysema. Five weeks before the present admission she had entered another hospital for treatment of increasing respiratory distress but had gradually lost ground. She continued to have frequent attacks of wheezing, lost weight, and became progressively weaker.

TABLE I. BLOOD GASES DURING CARBON DIOXIDE NARCOSIS*

Hospital Day	Clinical State	Serum CO_2 Content (Vol. %)	pCO_2 (mm. Hg)	pH	O_2 Capacity (Vol. %)	O_2 Per Cent Saturation
18**	Well oriented; breathing air	86.1	75	7.32	20.5	
19**	Well oriented; breathing air	84.0	74	7.31	18.2	
20	Unresponsive; on nasal oxygen	98.0	194	6.92	22.2	89.2
21	After 24 hrs. in respirator; on nasal oxygen; uncooperative; disoriented	75.5	59	7.37	16.2	97.6
23	Well oriented; breathing air	77.9	47	7.48	16.1	96.1
28	Well oriented; breathing air	67.3	45	7.44	18.8	94.2
45	Well oriented; breathing air	72.2	50	7.42	15.9	89.0

* Details of analytical methods have been presented elsewhere.[4] Carbon dioxide content was measured gasometrically, pH by glass electrode, and oxygen capacity and per cent oxygen saturation by a photometric method. pCO_2 was calculated from the other values.
** Venous blood (antecubital). Other samples are arterial.

Physical examination showed a tired, anxious, elderly appearing woman, who was moderately short of breath and preferred to sit up. The heart rate was 100 and the blood pressure was 140/90 mm Hg. She was not cyanotic. There was a moderate kyphosis, and the chest was markedly increased in antero-posterior diameter. The chest was hyperresonant, and the lung bases were low. Motion of the thoracic cage was very limited. Expiratory wheezes were heard over both lung fields. There was minimal ankle edema. The neck veins were not distended. The remainder of the physical examination was not remarkable.

Roentgenograms of the chest showed changes indicative of pulmonary emphysema. An electrocardiogram showed slight right axis deviation.

She was treated with bronchodilator drugs, mild sedation and breathing exercises, but she continued to be dyspneic and apprehensive. Eleven days after admission there was an episode of marked cyanosis and drowsiness. This cleared rapidly after the administration of parenteral caffeine and nasal oxygen. Thereafter, nasal oxygen was given intermittently.

About two weeks after admission her condition seemed to be deteriorating, and early on the morning of the seventeenth hospital day it was found that she could not be aroused. On the previous evening she had been given 1.0 grams of chloral-hydrate and 0.1 gram of pentobarbital, but she had tolerated similar sedation on several previous occasions. Nasal oxygen was being administered. The deep tendon reflexes were hypoactive. There was a lateral deviation of the left eye. The pupils were small, equal, and reacted to light. The blood pressure was 140/90 mm Hg. It was the impression of the house staff that she had had a massive cerebral vascular accident, and she was left on oxygen. Within three hours she was moving spontaneously, and four or five hours after this she had recovered completely and was alert and comfortable. A few hours later she was again somnolent, confused and moderately cyanotic without oxygen. It now seemed evident that the episodes of central nervous system depression were based on respiratory failure. Caffeine was administered on a regular schedule, bronchodilator drugs were continued, and antibiotics were started. She was digitalized, given diuretics, and started on a low sodium diet. Despite these therapeutic efforts she grew progressively weaker. Nasal oxygen was continued because she became markedly cyanotic without it. Venous blood samples on the eighteenth and nineteenth hospital days (Table I) showed a high serum carbon dioxide content but only a moderate depression of the pH.

On the morning of the twentieth hospital day she was found to be totally unresponsive and could not be roused even by painful stimuli. The blood pressure was 80/60 mm Hg. Nasal oxygen was being given. Examination of the arterial

blood (Table I) showed an extraordinarily high carbon dioxide tension and a markedly decreased pH, but there was only slight oxygen unsaturation. A considerable quantity of tenacious mucus was aspirated from the air passages under bronchoscopic guidance. ACTH was begun and was continued for the next week. Norepinephrine was given by intravenous drip intermittently during the next four days as needed to maintain the blood pressure at near-normal levels. Immediately after bronchoscopy the patient was placed in a Drinker respirator, where she remained for the next thirty-six hours. Nasal oxygen was continued. After twenty-four hours in the respirator the pCO_2 was greatly reduced and the pH had risen nearly to normal. When stimulated, the patient would open her eyes and struggle, but she would not respond to simple commands. After an additional twelve hours she was conscious but was still confused. At this point she was removed from the respirator and oxygen was stopped. She improved rapidly, and by the twenty-third hospital day the arterial oxygen saturation and pCO_2 were nearly normal while she was breathing air. The pH was slightly higher than normal. As indicated in Table I, the arterial blood values remained about the same on two subsequent examinations over a three-week period. She slowly gained weight and strength and was discharged on the ninety-sixth hospital day.

SUMMARY

A case is presented in which there were recurring episodes of confusion and coma resulting from pulmonary failure in a patient with asthma and emphysema. These episodes were apparently caused primarily by carbon dioxide narcosis which developed during oxygen therapy, although on two occasions drowsiness and confusion occurred while the patient was breathing air. The patient recovered spontaneously from one episode of profound coma, but treatment with a respirator was required on a second occasion.

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Submitted January 10, 1956

THE EFFECT OF LONG TIME FEEDING OF A SOYBEAN INFANT FOOD DIET TO WHITE RATS

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"THE construction of tissue proteins is an 'all or none' proposition, in the sense that the supply of amino acids for synthetic purposes is utilized only to the extent permitted by that amino acid available in the least amount with reference to the requirements of the protein pattern being followed. The amino acid supply does not appreciably modify the pattern of synthesis in any tissue, and incomplete or abnormal proteins are not formed to utilize better the amino acid supply presented to the tissues by the digestive tract."[14]

TABLE I.
CLASSIFICATION OF DIETARY AMINO ACIDS

Essential (Indispensable)	Semi-indispensable	Non-essential (Dispensable)
Histidine	Arginine	Glutamic Acid
Lysine		Aspartic Acid
Phenylalanine	Tyrosine	Alanine
Tryptophan		Proline
Methionine	Cystine	Hydroxyproline
Threonine	Glycine	Serine
Leucine		
Isoleucine		
Valine		

Histidine is not essential for healthy adult, non-pregnant humans. It may be essential for growth, new tissue formation and tissue repletion.

As a result of numerous investigations the amino acids may be classified into three dietary groups[3] as given in Table I. Arginine is classified as semi-indispensable because, while it can be synthesized to some extent by the growing rat from proline and glutamic acid and possibly other compounds, the rate of synthesis is not sufficient for the support of maximum growth. Tyrosine is formed from phenylalanine. However, since tyrosine is a usual constituent of tissue proteins, the dietary requirement for phenylalanine is reduced by the presence of tyrosine up to the amount required to cover the tyrosine needs of the organism. In like manner, cystine is furnished from the proteins of the diet, or it may be formed from methionine. Therefore, the dietary requirement for methionine is reduced by the presence of cystine up to the quantity required to cover the cystine needs of the animal.

On the basis of his own work and that of others, Mitchell[13,14] has developed the concept that the amino acid requirements of the growing animal are determined in the last analysis by the amino acid composition

From the Special Products Division of The Borden Company, New York, N. Y.

TABLE II. AMINO ACIDS IN GM. PER 16.0 GM. N
(VALUES TAKEN FROM REF. 2)

	Mull-Soy	Whole Milk	Whole Egg	Amino Acid Pattern Required by Humans Gm. of Amino Acid per 16.0 Gm. Nitrogen
Arginine	8.3	4.2	6.6	0.0
Histidine	3.7	2.6	2.4	0.0
Lysine	5.0	8.7	7.0	4.7
Tyrosine	5.2	6.0	4.5	—
Tryptophan	1.4	1.5	1.5	0.9
Phenylalanine	4.8	5.5	6.3	5.0
Cystine	2.3	1.0	2.4	3.3
Methionine	1.5	3.2	4.0	
Serine	5.1	4.3	7.5	—
Threonine	4.8	4.7	4.3	3.0
Leucine	7.3	11.0	9.2	7.1
Isoleucine	4.4	7.5	6.2	3.7
Valine	4.3	7.0	7.2	4.4
Glutamic Acid	14.2	21.5	12.0	—
Aspartic Acid	11.2	7.4	5.7	—
Glycine	4.2	2.3	2.7	—
Alanine	4.2	4.1		—

of the tissue proteins formed during growth, superimposed upon the amino acid requirements for replacement of the endogenous losses of nitrogenous material, i.e, for maintenance of the *status quo*.

The nutritional value of soy protein in hypoallergenic nutrition has recently received comment. Accordingly, it appears of interest to report upon a study of the comparative nutritional value of a soybean infant food (Mull-Soy® Powdered) and dried whole milk, in which the former was found to support reproduction and lactation over several generations of animals.

The excellent nutritive value of milk has long been recognized. Rats given raw milk supplemented with iron, copper and manganese as the sole source of food displayed normal growth and reproduction for five generations.[8] Processing of milk causes some loss in vitamin C and thiamine, but, if properly conducted, has little deleterious effect on the proteins.[5,11] The proteins of cow's milk are recognized to be excellent for the growth and well-being of human infants and of animals. Although it is true that the nutritive value of soybean proteins is not quite as good as those of milk, this fact is of no practical importance in infant nutrition. Table II gives the approximate amino acid composition of milk proteins, soybean proteins (Mull-Soy) and whole egg proteins calculated in grams of amino acid per 16 grams of nitrogen (conventionally 100 grams of protein). Whole egg proteins are recognized to contain amino acids in the most desirable pattern for human and animal nutrition. It will be seen from Table II that milk proteins compare very well in their amino acid composition with those of whole egg proteins, with the exception that both milk and soy proteins are slightly deficient in the sulfur amino acids, cystine and methionine. The fact that both milk and soy can be improved

slightly by the addition of either of these sulfur amino acids is also common knowledge. That soy proteins are a little more deficient in methionine than milk is of no consequence in practical infant feeding, for, as Mendel[12] pointed out many years ago, optimal growth and well-being can be achieved by supplying a larger quantity of a nutritionally inferior protein than would be necessary with a protein of higher biologic value, providing the inferior protein does not show any marked deficiency of an essential amino acid. This means that what is required is not a definite quantity of protein per day but a certain amount of each of the essential (and semi-essential) amino acids. As is seen in Table II, 100 grams of milk proteins will supply approximately 4.2 grams of cystine plus methionine, while soy proteins will furnish approximately 3.8 grams of these amino acids. Therefore, if one were concerned with feeding an infant the least amount of either milk proteins or soy proteins, then it would be necessary to supply approximately 11 per cent more of the soy proteins than milk proteins to achieve the same rate of growth.[4]

It will be seen in Table II that the quantity of lysine furnished by Mull-Soy is entirely adequate to supply a balanced amino acid pattern for humans.[2] The amino acid pattern of milk proteins shows an excess of lysine, among other amino acids. However, this surplus is wasted when milk is the sole source of food because the quantity of an essential amino acid which is used by the organism for new tissue formation or for the repair of the normal endogenous catabolic processes is in a fixed ratio with all the other essential amino acids.

In practical nutrition, a surplus of protein is always fed in the diet and clinical experience has repeatedly shown that infants thrive as well on soybean "milk" as on cow's milk.[6,7,9,10,15,17,18]

In order to study the effects of feeding a well-known soybean infant food for several life-cycles, the experiments described below were carried out. The object of these experiments was not to ascertain the protein efficiency of the soy product, but to feed it as the sole food to rats for several generations. The only supplements added to the commercial product were vitamins and iron, as are regularly recommended for infant feeding. As a control for these experiments, whole dried milk supplemented with the same vitamins and iron was also fed. It was recognized that the milk diet might be deficient in manganese and possibly in copper, and consequently the animals in this group were not expected to thrive as well as if the milk had been mineralized. However, in order to maintain a close relationship in the experiments to current infant feeding practice, neither diet was supplemented with minerals, other than iron.

EXPERIMENTAL

White rats, after weaning, were fed *ad libitum* a diet consisting of spray dried soybean infant food or whole dried milk, supplemented with the following:

	mg/100 g
Menadione	1.0
Thiamine hydrochloride	0.8
Riboflavin	1.6
Pyridoxine hydrochloride	0.8
Niacin	4.0
Calcium pantothenate	4.4
Para-aminobenzoic acid	4.0
Choline chloride	200.0
Inositol	21.6
Ferric citrate	120.0

Each animal was also given 500 I.U. of vitamin A, 100 I.U. of vitamin D and 0.5 mg of vitamin E (tocopherol) in oil weekly until mating, and then the same quantities twice each week. Typical analyses of the soy infant food and the dried milk used in the study are as follows:

Powdered Soybean Infant Food		*Dried Whole Milk*	
Protein (N x 6.25)	24.0%	Protein (N x 6.25)	26.0
Fat	30.0	Fat	28.0
Carbohydrate	35.9	Carbohydrate	37.7
Crude fiber	1.2		
Minerals	5.4	Minerals	5.8
Ca	1.0	Ca	1.24
P	0.9	P	.98
Fe	0.003	Fe	.0014
Moisture	3.5	Moisture	2.0

The general plan of the experiment was to mate one male with two females of different litters at ninety-nine days of age. If subsequent matings were desired, they were carried out three weeks *postpartum*. All litters were reduced to eight pups at the end of one week. This schedule was adhered to in the soy experiment, but could not be followed with the rats on dried milk due to the high mortality in the second generation.

The experimental results are summarized in Tables III and IV.

RESULTS

The data summarized in Table III show clearly that the soybean infant food supplemented with iron and vitamins permits good growth, reproduction and lactation for at least three generations. Thus it provides ample calories, protein and trace minerals for growth, reproduction and lactation of the rat for at least three generations and possibly more. The fact that rats fed soybean infant food grew as well as those on mineralized milk[1,16] indicates that, under practical conditions of infant feeding, soy proteins and milk proteins are interchangeable.

The results of feeding vitaminized milk plus iron are shown in Table IV. As was to be expected,[8] the copper and manganese deficiency of the milk began to show up in the second generation and completely prevented successful reproduction in the third generation.

TABLE III. RESULTS OF REPRODUCTION STUDY ON MULL-SOY RATION

Generation and Litter	Rat No.	Wt. of Female When Bred	No. Pups Born	Dead at Birth	No. Pups Weaned†	Av. 21 Day Wt. of Pups	Daily Gain 7-21 Days	Weekly Gain of Pups 3-9 Weeks	
								Male	Female
1st generation, 1st litter	MA1	181	9	0	8	37.4	—	26.2	17.1
	MA2	186	10	1	8	39.6	—	32.3	20.2
2nd generation, 1st litter	MB9	165	11	0	8	38.1	1.9	22.5	15.8
	MB10	176	12	0	8	34.0	1.6	29.7	17.8
	MB4	200	12	2	8	29.6	1.2	27.3	18.2
	MB5	203	10	0	8	42.7	2.0	27.7	16.5
2nd generation, 2nd litter	MB9	199	11	2	8	47.5	2.3	—	—
	MB10	209	12	1	8	45.4	2.3	—	—
	*MB4	237	12	1	0	—	—	—	—
	MB5	238	13	1	8	44.9	2.1	—	—
2nd generation, 3rd litter	*MB9	228	9	0	0	—	—	—	—
	MB10	231	9	0	8	38.4	2.0	—	—
	*MB4	284	11	0	0	—	—	—	—
	MB5	276	11	5	4	39.5	2.3	—	—
3rd generation, 1st litter	MC18	163	9	1	8	36.0	1.9	—	—
	MC20	166	12	3	8	37.1	2.4	—	—
	MC8	174	11	1	8	30.75	1.5	—	—
	MC9	184	11	2	8	29.6	1.2	—	—
	MC3	185	12	2	8	43.0	2.1	—	—
	MC5	185	10	1	8	32.6	1.4	—	—
	MC14	179	13	4	3	46.3	2.7	—	—
	MC15	188	9	0	5	40.0	2.2	—	—

*All pups died by one week as a result of no milk from dam.
†When in excess all litters cut to eight at one week of age.

TABLE IV. RESULTS OF REPRODUCTION STUDY ON MILK RATION

Generation and Litter	Rat No.	Wt. of Female When Bred	No. Pups Born	Dead at Birth	No. Pups Weaned†	Av. 21 Day Wt. of Pups		Weekly Gain of Pups 3-9 Weeks	
								Males	Females
1st generation, 1st litter	KA1	196	13	0	8	31.6	Daily Gain from 7-21 days not recorded	29.3	16.9
	KA2	194	7	0	7	35.3		26.4	17.8
2nd generation, 1st litter	*KB4	185	5	1	0	—		—	—
	*KB5	170	7	2	0	—		—	—
	KB9	176	7	0	5	44.0		21.2	16.5
	KB10	181	11	3	6	34.7		18.9	16.0
2nd generation, 2nd litter	*KB4	225	11	0	0	—		—	—
	*KB5	222	10	0	0	—		—	—
	*KB9	236	9	2	0	—		—	—
	KB10	253	12	1	4	23.5		—	—
2nd generation, 3rd litter	KB4	No pregnancy							
	KB5	No pregnancy							
	*KB9	248	6	2	0	—		—	—
	KB10	No pregnancy							
3rd generation, 1st litter	KC10	No pregnancy after 70 days with male							
	*KC4	179	5	0	0	—		—	—
	KC5	No pregnancy after 70 days with male							

*All pups died or were eaten within one week. Little or no milk from these dams.
†When in excess all litters cut to eight at one week of age.

SUMMARY

1. Mull-Soy supplemented with iron and vitamins will support excellent growth, reproduction and lactation in white rats for at least three generations.

2. It is entirely adequate as sole source of proteins, fats, calories, trace minerals and unidentified nutrients when suitably supplemented with recognized vitamins and iron.

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Submitted December 19, 1955

THE USE OF A NEW RESPIRATORY INDEX FOR THE EVALUATION OF XANTHINE DRUGS IN CHRONIC PULMONARY DISEASE

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THE evaluation of drugs for the treatment of bronchial asthma and emphysema is difficult in the absence of accepted standards. For this reason, new techniques of comparing symptomatic benefit and objective changes after drug treatment merit careful consideration.

As a means of evaluating and grading the cause and severity of dyspnea, Gross[4] recently devised a respiratory index (RI) which is defined as follows:

$$RI = \frac{\text{Vital Capacity (ml)}}{100} + \text{breath-holding time (seconds)}$$

It is based on the studies of Herrmann[5] and White[9] of vital capacity and of breath-holding time as tests of the functional state of the circulatory system. These tests are not related to each other, and therefore, yield independent information. Vital capacity represents a true picture of clinical status and pulmonary function, as it is little affected by psychic factors. Breath-holding capacity, on the other hand, is a complex function and can be affected by many factors, including psychic ones, and therefore reflects the somatic as well as the psychic state of the patient.

Gross believes that his index closely correlates with the presence and severity of dyspnea and that it provides the most practical and reliable clues to the state of the dyspneic patient and refers to function and not anatomical condition.

Based on a large series of patients, Gross developed the following scale (see Graph I):

70 or better—Patient normal—dyspnea absent.

60 - 70 —Patients with heart disease in improved functional condition; also found in healthy individuals with limited respiratory capacity—occasional dyspnea.

30 - 60 —Dyspnea due primarily to impaired heart function.

20 - 36 —Severe dyspnea usually due to chronic pulmonary disease.

It was felt that this index would be useful in (1) classifying and following a group of geriatric patients chronically ill with pulmonary emphysema, bronchitis and asthma, and (2) observing the effectiveness of various drug therapies.

Brown[1] observed that choline theophyllinate was useful in patients

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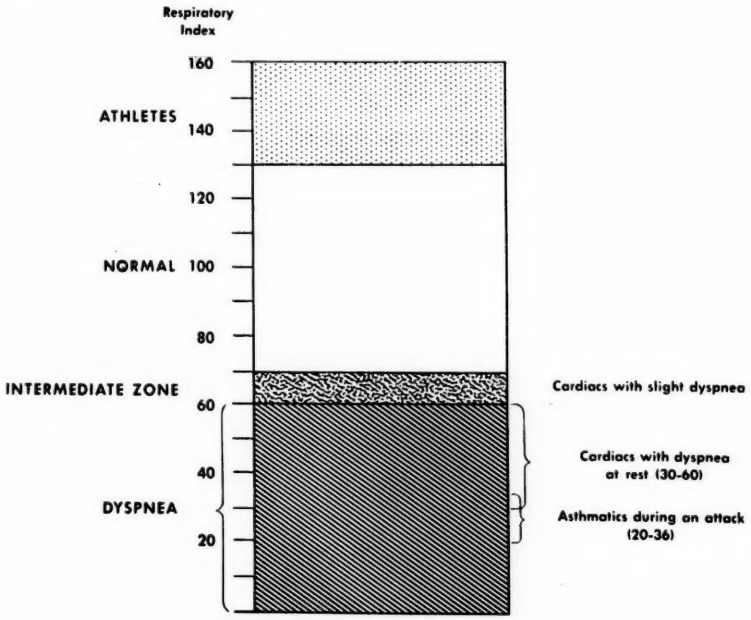
Presented at the Twelfth Annual Congress of The American College of Allergists, New York, New York, April 18, 1956.

requiring respiratory stimulation. In Brown's study, as well as in previous ones,[2,3,6,7] choline theophyllinate was reported as: (a) being effective in preventing asthmatic attacks; (b) being well tolerated, even in large doses; and (c) not losing effectiveness when used over long periods



Graph I.

of time. Brown observed that the older patient with bronchitic or emphysematous asthma responded best to this medication.

It appeared that an opportunity was thus presented to test the value of the respiratory index by comparing objective changes following choline theophyllinate therapy with symptomatic improvement. Also, since the value of oral aminophylline preparations had not been established fully as reliable or consistent oral therapy for asthma, this drug was included in the study.

THE TEST METHOD

The respiratory index was obtained by combining the vital capacity and the breath-holding time data as described by Gross. Vital capacity was determined in the upright position, with the McKesson-Scott apparatus, timed at three seconds, and using the best of several times. The breath-holding test was carried out in the same position, measuring the maximal duration of inspiratory apnea.

In order to be certain that our index closely approximated the results reported by Gross, we did a preliminary evaluation on some of the attendants and nurses on the wards and found that the respiratory index of these average individuals ranged anywhere from 70 to about 115, whereas Gross reported a range of 71 to 160. There was still a marked difference between the results obtained in this normal group and those of the patients with emphysema and bronchial asthma.

THE PATIENTS

The patients included in this series are mostly World War I veterans chronically ill with pulmonary emphysema, chronic bronchitis and asthma. They presented all the typical signs and symptoms of intractable asthma and chronic pulmonary disease.[8]

The patients ranged in age from forty-three to seventy-five years, the average being fifty-seven. The mean duration of disease was eighteen and one-half years. All had received the usual antiasthmatic drugs such as bronchodilators, expectorants, et cetera, with little effect. All had a chronic cough productive of one-quarter to one cup of thick grey, yellow or green sputum every twenty-four hours. Most of the patients complained of shortness of breath and wheezing on mild exertion or change of position, which was partially relieved by productive cough or rest. There appeared to be no seasonal or geographical factors; however, damp weather or acute respiratory infection did in some instances augment the severity of the condition. The symptoms seemed to be worse on arising in the morning. In only a few instances was there any personal or family history of allergy. This group was considered suitable for testing a new drug because any improvement would be noted both subjectively and objectively as compared to the previous state. It was felt that the patients could serve as their own controls since they had been under observation for quite some time.

There were two groups of patients: (a) Fifty patients who had not had xanthine medication in the preceding six months were chosen for objective evaluation. Three agents were employed in this part of the study: placebos, aminophylline, and choline theophyllinate* and each patient received, on a blind basis for a period of one month, each of the three preparations, in varying order. Respiratory index and blood pressures were taken before and after the administration of each of the three drugs. The objective change was based on the difference between two RI values. Comparison of the therapeutic effect of each of the agents was based on the amount of change in the RI. Other medications and vaccines, inhalant allergens, et cetera, were used throughout, as indicated. (b) 150 patients, similar in type to those just described, were treated with choline theophyllinate (200 mg. four times daily) in addition to

*Choline theophyllinate (Choledyl®) supplied by the courtesy of Nepera Chemical Co., Inc., Yonkers, N. Y.

any other indicated medication. In this group the RI was not determined and the response to the drug was judged entirely by symptomatic relief as reported by the patients. These were observed primarily as to the alleviation of symptoms produced by choline theophyllinate in this condition. We did not select another group of 150 patients for treatment with oral aminophylline because previous experience had shown that this agent produced a high degree of gastric irritation, and therapeutic response had been equivocal.

TABLE I. R. I. CHANGES FOLLOWING THERAPY

	Average R.I.	Percentage of Patients Showing Increase	Amount of Increase	Percentage of Patients Showing Decrease	Amount of Decrease
Before Therapy	40.5				
After Placebo	36.0	33	3—20	66	0—13
After Amin.	44.5	50	2—20	50	0— 8
After Chol. Theo.	47.7	75	1—18	25	0— 7

RESULTS

A. *Group of Fifty Patients.*—The respiratory index prior to medication ranged from 19 to 69, the lower figure indicating more severe dyspnea on mild exertion. The average RI value at the beginning of the test was 40.5. Each of the patients was started on either the choline theophyllinate, aminophylline, or placebo. The medications all looked alike, the dosages were the same for each, one tablet four times daily (or 200 mg of choline theophyllinate or aminophylline) so as to offset any possible psychologic effect. Medication was continued for one month on each and the RI repeated. The blood pressure findings for this group were divided as follows:

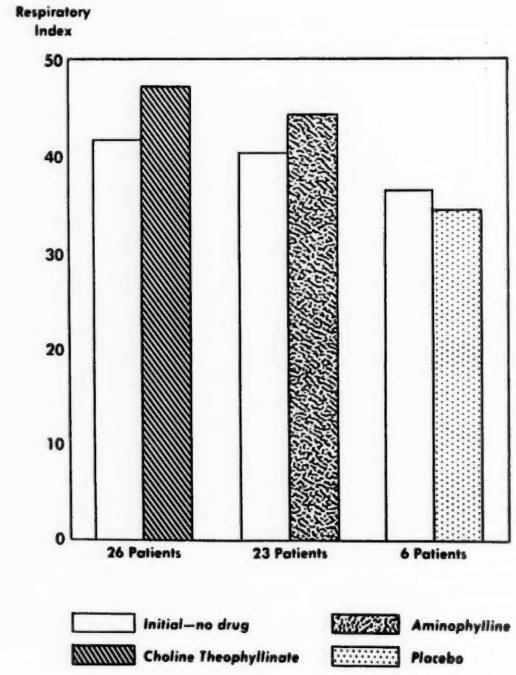
$$\text{Normotensives } \frac{(125 - 135 \text{ mms})}{(70 - 80 \text{ mms})} \text{ 28, hypotensives 7, hypertensives 15.}$$

Any index of pulmonary function has to deal with individual variation. Acute respiratory infection, the condition of the weather, or the fact that a few patients have difficulty holding their breath due to practically constant cough have not been considered. These variants, however, would tend to equalize over the course of three months on the fifty patients studied.

1. *Results on Aminophylline.*—Fifty per cent of the patients showed an increase in RI of from 2 to 20, the other half no change, or a drop in index which ranged from 1 to 30 (Table I). When aminophylline was the first drug given, the mean initial increase in RI was 4.13, the range being —10 to +22 (Graph II). When aminophylline was given following choline theophyllinate therapy, the mean increase in RI was 0.86 ranging from —8 to +20 (Graph III).

In this group many patients reported subjective relief. Dyspnea was

reduced but the thick inspissated sputum was unchanged. Early morning coughing and wheezing were still present in the majority of patients. Of the twenty-eight normotensive patients treated, eleven showed minimal drops in blood pressure, eleven showed no change, and seven small

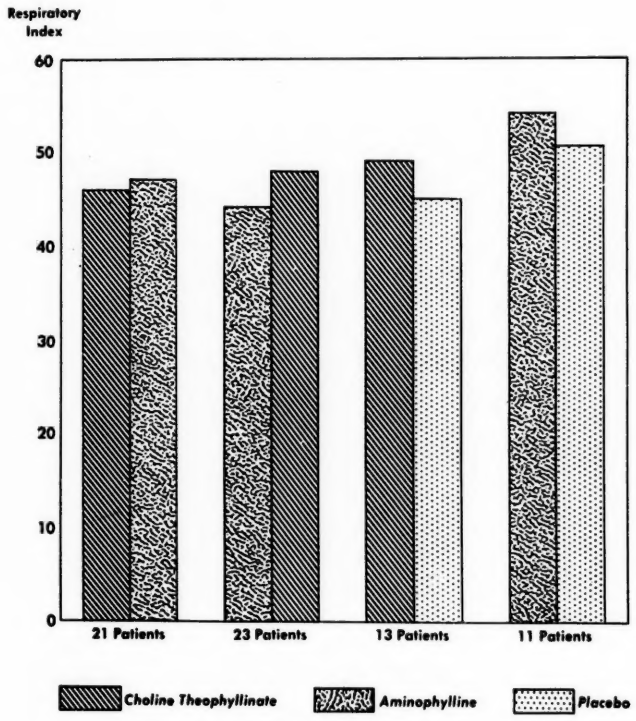


Graph II.

increases. Only two of the eleven patients with hypotension showed any change. When the increase in RI was marked, there appeared to be a drop in systolic and diastolic blood pressure in the hypertensive and a rise in the hypotensive, while the normotensive showed no change. Seven patients complained of marked gastric symptoms on this medication.

2. *Results on Choline Theophyllinate.*—Seventy-five per cent of the patients had an increase in RI ranging from 1 to 18, while the remaining 25 per cent had no change, or a drop of up to seven (Table I). When choline theophyllinate was given as the first agent in the study, the change from the initial level was a mean increase of 5.46 in the RI, the range of change being from —6 to +18 (Graph II). When choline theophyllinate was given following aminophylline, there was a mean increase in RI of +3.65. The range of change was from —13 to +29

(Graph III). The patients in many instances reported marked improvement. Dyspnea diminished and a few patients were even able to undertake light work. The incidence and severity of wheezing and cough was reduced. Many patients were able to expectorate more easily as the sputum



Graph III.

apparently became less viscous. However, x-rays of the chest remained unchanged.

As to blood pressure: of the twenty-eight normotensive patients, twelve showed minimal reduction; of the fifteen with hypertension, four showed small increases, and one a drop. There appeared to be no definite correlation between improvement in pulmonary function and change in blood pressure.

Two patients reported mild nausea while taking this drug, but not of such severity as to necessitate discontinuance.

3. *Results on Placebo.*—Two-thirds of the patients showed no change or a drop in RI up to 13 following placebo therapy. The remaining third showed slight increases ranging from 1 to 4 (Table I). When the place-

bo was given at the start of the study the average change was —1.83, the range being from —13 to +6 (Graph II). When the placebo was given following aminophylline the average change was —3.73, ranging from —26 to +3. When given following choline theophyllinate the average change was —4.00 ranging from —23 to +9 (Graph III).

When the placebo followed the xanthine, the respiratory index did not return to the original level. This may have been due to the continuation of xanthine effect following cessation of medication.

Very few patients showed any improvement in subjective findings on placebo. All reported continuance of cough and shortness of breath, particularly on arising, thick phlegm difficult to expectorate, and on physical and x-ray examination there was no change. There was no real blood pressure variation. However, three patients with hypertension, who obtained marked increases in RI, had significant lowering of blood pressure. No gastric intolerance was reported.

B. Group of 150 Patients.—Choline theophyllinate was added to the usual therapeutic regimen to see if there would be an increase in symptomatic relief. After about two to three weeks on this agent, many patients stated voluntarily that they felt better. They did not appear to be as short of breath as previously, coughed less, brought up sputum with greater ease, and were generally improved. Blood pressure was lower in about 50 per cent. Most have continued to request this medication. About 13 per cent of these 150 patients failed to report improvement and three complained of gastric irritation.

DISCUSSION

In the group of fifty patients, symptomatic changes paralleled the fluctuations in the RI. Since each drug was employed for one month, it was felt that the index demonstrated the long-range drug effect rather than immediate drug action.

Although improvement or change in RI is not very large, the changes do have statistical significance (level $> .1$ per cent and are noted in Table II). The chronicity of the illness and the relatively short duration of treatment may account for this. However, in many individual cases, the improvement in the RI probably indicated marked therapeutic effect.

The second group of patients reacted symptomatically to choline theophyllinate in the same way as the smaller group. Thus the RI of Gross can be employed to test quickly the effect of a new drug in conditions causing dyspnea. Complex apparatus is not required, the test can be performed easily, and appears to be a satisfactory index of pulmonary function.

A review of the results with two xanthine drugs and with a placebo indicates that the patients definitely were improved, both subjectively and objectively, on the xanthines. The choline salt of theophylline ap-

TABLE II. CHANGES IN R. I. DURING MONTH OF THERAPY FOLLOWING PREVIOUS THERAPY

Previous Therapy	Therapy Given	Mean Change	Statistical Significance*
Initial—no drug	Choledyl	+5.5	S
Initial—no drug	Aminophylline	+4.1	S
Initial—no drug	Placebo	−1.8	O
Choline Theophyllinate	Aminophylline	+0.9	O
Aminophylline	Choledyl	+3.7	O
Choline Theophyllinate	Placebo	−4.0	O
Aminophylline	Placebo	−3.7	O

*Level of Significance >0.1%
S = significant
O = not significant

parently was more efficient in producing both types of improvement than was aminophylline. A greater number of patients obtained increases in RI with choline theophyllinate than with aminophylline. In chronic lung disease, improvement is quite limited. The results obtained in the group of 150 patients paralleled those in the smaller group and demonstrates the value of the test as a means of evaluating a new drug in a small group and in a comparatively short period of time.

One of the results observed was that when choline theophyllinate was given following aminophylline, there was a noticeable rise in RI which did not occur when aminophylline was given following choline theophyllinate. However, because of the small number of cases and wide range of effects, this difference was not of statistical significance. Another interesting observation was the effect of placebo on the RI. When it was based on the initial level there was an apparent increase in RI of 3.27. This indicates an apparent carry-over of xanthine action since the placebo period usually followed one or two months of xanthine therapy.

The experience with the large group receiving the new choline salt of theophylline proved to be worthwhile in two respects. It confirmed the impression of the usefulness of the RI as a means of judging a drug's therapeutic value, and also indicated that choline theophyllinate benefited the emphysematous individual. Choline theophyllinate was extremely well tolerated. It is quite likely that when the xanthines fail to give relief from dyspnea it is often not because they are therapeutically ineffective, but because they fail to be tolerated in large enough doses.

Therefore, choline theophyllinate should be quite effective in the oral treatment of chronic bronchial asthma and emphysema. Intravenous and rectal forms of aminophylline or theophylline are more suitable for the acute attack.

Blood pressure changes were of particular interest because a preliminary study had indicated a possible relationship between improvement in RI and adjustment of the blood pressure toward normal levels. It was suspected that the hypotensive effect was related to the improvement in pulmonary circulation and pulmonary function. However, results in

this study failed to show any correlation between change in the peripheral blood pressure and improvement in the chronic pulmonary disease as demonstrated by increase in the RI.

CONCLUSIONS

1. In a series of fifty patients with chronic pulmonary emphysema and chronic asthmatic bronchitis, the new respiratory index described by Gross was found to be an efficient and easy method of determining objectively the amount and severity of dyspnea. This is a practical way of evaluating new therapeutic agents in these conditions.

2. Comparative studies in fifty patients demonstrated that they had greater relief of dyspnea on oral xanthines than when on placebo.

3. In the same fifty patients, oral choline theophyllinate was more effective than oral aminophylline as shown by symptomatic improvement and increase in respiratory index. In the same dosage, this new choline salt of theophylline produced far fewer gastrointestinal symptoms.

4. A second series of 150 patients with chronic emphysema and chronic asthmatic bronchitis was treated with choline theophyllinate. The therapeutic results corresponded with those obtained in the first group.

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Submitted Dec. 27, 1955.

A NEW ANTIHISTAMINE WITH MINIMAL SIDE EFFECTS

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DROWSINESS has been one of the major annoyances of antihistaminic therapy. Nearly all the compounds in use today cause some degree of drowsiness ranging from very mild to severe. In a recent article, Galambos[5] emphasized this very point by noting it is, "evident that all antihistaminics possess side effects, most important of which are sedation, drowsiness and sleepiness." Such reactions, in many cases, nullify or delimit the usefulness of antihistaminics. According to Cooke,[2] "side effects such as somnolence limit the amounts that may be required to control symptoms."

New and Nonofficial Remedies for 1954[6] points out that other side reactions such as "inability to concentrate, dizziness and disturbed co-ordination are related to sedative action" and only add to the difficulties of antihistamine administration. These by-effects are particularly dangerous in individuals who operate machinery, drive cars or who must remain alert during their working hours.

In view of this situation, any preparation which could eliminate or reduce drowsiness to a minimum would be a worthwhile addition to antihistamine therapy. A new preparation was brought to our attention which was reported to eliminate to a great extent this antihistamine drowsiness. It is Plimasin,® a combination tablet which contains a cerebral stimulant, Ritalin,® (Methyl Phenidylacetate, Ciba) with the widely used, highly effective antihistamine, Pyribenzamine,® (Tripelennamine hydrochloride, Ciba).

Plimasin contains 25 mg of tripelennamine hydrochloride and 5 mg of methyl phenidylacetate. The analeptic qualities and safety of methyl phenidylacetate have been demonstrated in the literature. It has an action midway between caffeine and amphetamine.[8] The combination has been used clinically by others[7] and reported to be very effective with an almost negligible sedative action. According to Arbesman,[1] "the usual sedation seen with antihistaminics is almost absent."[4]

We selected 105 patients with allergic rhinitis, ranging in age from five to fifty-two years, who were unable to take antihistaminic agents, particularly because of drowsiness. At the completion of the study, we found that only three patients (2.8 per cent) complained of drowsiness, while ninety-two patients (87.6 per cent) had no side effects whatsoever (Table I).

We obtained fair to excellent relief in ninety-two patients and less than 25 per cent or no relief in thirteen. (Table II). The average dosage was

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Dr. Sievers is Chief of the Allergy Service, Los Angeles Children's Hospital.
Plimasin supplied through the courtesy of Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE I. SIDE EFFECTS

Type	Number of Patients	
None	92	
Insomnia	4	(high doses)
Drowsiness	3	
Nausea	2	
Headache	2	
Shakiness	1	
Restlessness	1	
	105	Total

TABLE II. RELIEF WITH PLIMASIN

Excellent	(75-100%)	8
Good	(50- 75%)	47
Fair	(25- 50%)	37
No relief	(25% or less)	13
		105 Total

four tablets a day in sixty-one patients and three tablets a day in the remaining forty-four.

Most of the patients reacted well to the preparation. The clinical results were what one would expect of a good antihistamine with the added advantage of little or no drowsiness.

SUMMARY AND CONCLUSION

Plimasin, a new preparation for antihistamine therapy, was studied for its relative effectiveness and possible elimination of the usual drowsiness caused by most antihistaminic preparations.

It was used in 105 patients having allergic rhinitis. Ninety-two demonstrated fair to excellent relief, and only three of the 105 complained of any drowsiness.

The new preparation, a combination of an analeptic and a well-known, clinically effective antihistamine, was found to be an effective antiallergic with the additional advantage of having little or no sedative action, and represents another useful combination of an antihistamine and an analeptic drug.

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CONTINUOUS STEROID HORMONE TREATMENT OF CHRONIC ASTHMA

I. Cortisone and Hydrocortisone

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IT has been well established during the past five years that cortisone and hydrocortisone in adequate dosage will produce dramatic remission in cases of asthma, atopic eczema and severe pollenosis. These steroids have also been used successfully in treating other allergic conditions, such as drug allergy, serum sickness, contact allergy, urticaria and ocular allergies. In addition to these clearly allergic diseases, cortisone and hydrocortisone have been of value in treating such conditions as rheumatic fever, emphysema, nasal polyposis, iritis, and collagen diseases, in which the role of hypersensitivity is not entirely clear.[1,2,3,6,8,14]

Only rarely does a permanent cure in a chronic allergic disease follow a short period of treatment. Relapse is the rule within a few days or weeks after the steroid is discontinued. Repeated courses of treatment are likely to be progressively less effective, and recurrences more severe.[2,3,6,8] These cases require continuous treatment, so that the problem becomes one of selecting the most effective routine that will suppress symptoms and at the same time minimize or control undesirable side effects.

In treating self-limited allergic states such as serum sickness, drug reactions or severe pollenosis, side effects of the adrenal steroids do not present much of a problem.[12,17,18,21] With continuous treatment, however, the side effects can be a major factor. The undesirable metabolic, endocrine and immunologic effects,[19,20] together with appropriate control measures,[7,11] are reviewed in Table I. Both prednisolone and hydrocortisone are improvements over cortisone in regard to severity of side effects in the treatment of allergic disease, but even with these precautions must be observed.

CASE MATERIAL

Our patients may be divided into three groups. The "Cortisone Group" was treated from January, 1953, to August, 1954, with cortisone and

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We wish to express our thanks for materials used in this study to the following companies: Merck and Co., and Upjohn Co., for cortisone and hydrocortisone; White Laboratories, for Dienestrol; Eli Lilly and Co., and Riker Laboratories, for potassium salts; Schering Corp., for Prantal; G. D. Searle and Co., for Probanthine; Ciba, Inc., for methyltestosterone.

TABLE I. PHYSIOLOGIC "SIDE EFFECTS" OF CORTISONE AND METHODS OF CONTROL

A. Effects for Which Adjuvants Were Given Routinely

Physiologic Effect	Control Measures
1. Sodium retention and edema	Low sodium intake
2. Potassium loss	Potassium salts by mouth
3. Psychic disturbance	Potassium salts by mouth
4. Functional adrenal cortex atrophy	Androgens and ascorbic acid
5. Protein catabolism and nitrogen loss	Androgens, estrogens and increased dietary protein
6. Pepsinogenesis, gastric hyperacidity and ulceration	Anticholinergics and antacids

B. Effects Treated When and If Indicated

Physiologic Effect	Control Measures
1. Lowered resistance to infection	Antibiotics in full doses
2. Excessive weight gain	Low calorie diet and dextroamphetamine
3. Hypertension	Sedation, antihypertensive drugs
4. Hyperglycemia	Insulin, diet control
5. Thyroid depression	Dessicated thyroid by mouth
6. Activation of tuberculosis	Withdrawal of cortisone, and anti-tuberculous drugs
7. Hirsutism and virilism	Estrogens
8. Acne	Local skin care

adjuvants. From August, 1954, to March, 1955, a portion of this original group was transferred to hydrocortisone, and is referred to as the "Transition Group." A third or "Hydrocortisone Group" consists of cases newly treated with hydrocortisone from August, 1954, to March, 1955.

The patients selected for this study all had chronic allergic disease, by which is meant that symptoms had been continuously present for two years or more. The shortest duration of principal complaint in any patient was two years; the longest was forty-five years, with the median at seven years.

In addition to chronicity of disease each patient was not responding satisfactorily to the usual allergic management. This consisted of desensitization when appropriate, bronchiolar relaxing agents such as epinephrine, ephedrine, and aminophylline in various forms, potassium iodide and other expectorants, antihistamines, antibiotics, sedation, diet and environmental control (and in the case of neurodermatitis, local treatment of the skin). The minimum length of treatment before this study began (in January, 1953) was one year, with the median at three and one-half years. In all, fifty-two patients from clinic and private practice took part in the study. Forty-seven had asthma with or without emphysema, and five had neurodermatitis. There were fifteen children under twelve years of age and thirty-seven adults.

CORTISONE GROUP

Thirty-two patients were treated with cortisone and adjuvants to control side effects. There were twenty-seven cases of chronic asthma and five cases of chronic neurodermatitis. In this group seventeen patients were treated for twelve to eighteen months, thirteen cases treated for six to twelve months, and two cases less than six months. The average for the entire group was 11.9 months.

Patients were checked routinely at regular intervals for weight, blood pressure, condition of lungs and heart, and the presence of edema, moon face, acne and hirsuitism. In addition, a chest x-ray, complete blood count, urinalysis and protein-bound iodine were taken at regular intervals.

Throughout treatment each patient kept a daily chart recording the number and severity of symptoms, the amount of steroid taken, and any other medication used to control symptoms. These charts provided a check on the patients' own opinion of the results obtained.

Cortisone Dosage.—The initial dose of cortisone on adult clinic patients varied from 150 to 300 mg per day in divided doses, with the majority starting at 200 mg. If symptoms did not respond, this was increased in some cases to 400 or 500 mg. Private patients were started on cortisone at 100 to 300 mg per day with proportionately more at the higher dose than was the case with clinic patients.

Children were started on proportionally lower doses ranging from 100 to 200 mg per day—the majority at 100 mg per day.

Cortisone was held at the initial level for one or two weeks, then reduced from the higher doses to 150 or 100 mg daily for another two to three weeks. Following this, an attempt was made in each case to find the lowest maintenance dose that produced satisfactory control of symptoms. In adults this ranged from 50 to 100 mg per day; in children 37.5 to 50 mg per day. Attempts to go below these figures usually resulted in prompt return of symptoms. Relapses following a previously satisfactory course were treated by raising the daily cortisone dose by 50 to 100 mg until a favorable response occurred, after which the dose was reduced again gradually. Whenever infection seemed to play a role in a relapse, antibiotics were administered in full dosage, and were often effective even when the dose of cortisone was not increased.

Adjuvants Used with Cortisone.—Patients were put on the following routine:

1. Advised to refrain from salt in cooking or eating salted food.

2. Given potassium chloride or triple potassium salts to provide 2 to 6 grams daily.

3. Given anabolic agents; adults took .05 mg Dienestrol® and 10 mg testosterone daily; children took .01 mg Dienestrol and 2 to 5 mg testosterone daily.

4. Given anticholinergics; either 100 mg Prantal® or 15 mg Probanthine® three times a day. (Children proportionally smaller doses).

Adjuvants were gradually reduced but not discontinued as cortisone was reduced to the maintenance level.

Testosterone was given both for its effect in reducing nitrogen loss, and its partial effect in preventing adrenal atrophy.[7] Both estrogen and

testosterone have a further value in minimizing loss of calcium and phosphorus.[10]

The anticholinergics were used to control pepsinogenesis and excessive gastric acidity and decrease the danger of ulcer formation. If epigastric pain appeared before meals, aluminum hydroxide was used as a supplementary precaution.

It was not found necessary to use thyroid extract, insulin or hypotensive drugs.

Nonspecific measures to combat side effects included diuretics and dextroamphetamine. Four patients were given short courses of Mercuhydrin® injections to reduce excessive edema. The results were not striking. Dextroamphetamine was used without much success by several women patients to control the weight gain that accompanied cortisone treatment.

Routine Allergic Treatment.—During the cortisone study patients were continued on whatever desensitization schedule had been followed previously. They were permitted to use their customary medication whenever they felt the need for it. The amount of medication used was considered in each case when evaluating the result of cortisone treatment. That is, the patient's subjective estimate of his condition was checked against his daily record of medication taken.

Results.—

1. *Excellent:* Three patients (9 per cent). Two cases of asthma and one of neurodermatitis had complete relief of symptoms without undesirable side effects. The adults with asthma were maintained on 37.5 and 50 mg cortisone daily. The child with neurodermatitis required 25 mg daily.

2. *Good:* Eighteen patients (56 per cent). Seventeen with asthma and one with neurodermatitis were symptom free for long periods, ranging from several weeks to six months, but showed occasional relapses that responded to temporary increase in medication. Intercurrent infections, exposure to allergens, unusual exertion or emotional crises were the common causes of a relapse. Daily maintenance doses in this group were: five (all children) on 25 to 37.5 mg, six on 50 mg, five on 75 mg, one on 100 mg and one (a case of severe neurodermatitis) on 225 mg.

3. *Fair:* Eight patients (25 per cent). The asthmatic patients in this group had had their disease for twenty or more years, with emphysema as a complication in all. These patients continued to have symptoms though not as severely as before, and used less of their customary medication. Doses of 200 to 400 mg of cortisone daily failed to relieve symptoms completely. The average maintenance dose of cortisone was higher in this group as compared to the group with "good" results, namely 106.3 mg as against 65.3 mg.

4. Poor: Three patients (9 per cent). These asthmatic individuals did not respond to the initial dose of cortisone after several weeks of treatment.

The excellent and good response cases together numbered twenty-one, or 63 per cent of the total, and 90 per cent showed some improvement. There was little difference between the results in the private and clinic patients. Private cases showed 73 per cent good to excellent relief, whereas the clinic group showed 60 per cent. With the small numbers involved it is doubtful if this difference is significant.

Complications and Side Effects.—In our study the severe complications usually thought to accompany continuous cortisone treatment did not appear.

There were no instances of emotional disturbance,[15] uncontrolled hypertension, glycosuria, thyroid depression, activation of gastrointestinal ulcer[9] or tuberculosis,[5] bone demineralization with fracture,[4] or severe masked infection.

Blood pressure changes were not striking. Among the clinic patients, the average systolic rise was 15 mm Hg, the diastolic 9 mm Hg. The greatest rise encountered was 28 mm Hg in one clinic patient, and the greatest diastolic was 40 mm Hg in one private patient. In twenty patients on whom pressure readings were made regularly, pressures at the end of the study were the same or lower than at the start.

Weight gain, on the other hand, was present in almost every case and pronounced in the majority. Weight gain usually began within a week and rose rapidly while the patient was on high doses of cortisone. Weight fell off as cortisone dosage was reduced, but tended to rise again later even on low maintenance doses. Primary weight gain appeared to be related to water retention, was accompanied by clinical edema in 50 per cent of the patients but did not respond to diuretics or low salt diet. The secondary rise appeared to be due to increased food intake. The most striking gains were in children; two gained 69 per cent of their initial weight in one and one-half years, three gained 40 to 46 per cent, and four better than 25 per cent. There was a sex difference in weight gained. In males the average was 10.3 per cent, in the females 26.6 per cent of initial starting weight. The actual amount these patients were over ideal weight ranged from none to 20 per cent, with the average at 9 per cent.

Although no direct attempts were made to measure adrenal function during the study, such as the eosinophil response to ACTH, there was indirect evidence of no serious adrenocortical impairment.[13] None of the patients complained of more than transient asthenia after cortisone was discontinued temporarily.

Surgery was performed on five patients at some time during their

cortisone treatment. Two children had tonsillectomies, one child and one adult had hernial repairs, and one an appendectomy. One other case suffered a simple fracture of the forearm from a severe fall. In each case the dose of cortisone was increased by 50 to 100 mg per day from the day before operation to three or four days afterward.

One adult patient had a submucous resection a month after cortisone was discontinued without any supportive cortisone treatment.

Nineteen patients were given fifty-six courses of antibiotics to control respiratory infections. Indications for antibiotic treatment were recurrence or sudden increase of asthma, whether accompanied by fever or not, during the respiratory infection "season," and the appearance of infected sputum in a patient previously raising clear mucus. In most cases the antibiotic controlled the asthma without the necessity of increasing cortisone dosage.

One patient, a sixty-nine-year-old woman, suffered reactivation of an old osteomyelitis of the hip which had been present and occasionally draining since childhood. This abscess was drained surgically and healed after one month on streptomycin, which was given in daily doses of one gram. Cortisone was continued during and after the episode.

Chest x-rays on this group did not show any significant changes. Protein bound iodine averaged 3.8 mcg/cc at the start of the study in the cortisone group, and 3.9 mcg at the end of six months. These values are within normal limits with the method of assay used.

TRANSITION GROUP

Twenty-two of the thirty-two patients previously on cortisone were placed on hydrocortisone, at which time all adjuvant therapy except potassium salts was discontinued. None of the patients who had responded poorly to cortisone was included in this group. Otherwise it resembled the cortisone group in severity of disease and age distribution.

Each patient continued to keep the daily record of symptoms and medication. As before when on cortisone, patients were checked for weight, blood pressure, edema, chest x-ray, blood counts and urinalysis, but at less frequent intervals. This was possible because satisfactory control of symptoms was obtained at lower doses of hydrocortisone, as will be seen below.

Hydrocortisone Dosage.—In transferring these patients, the initial dose of hydrocortisone was 20 per cent less in milligrams than the current amount of cortisone being used. That is, for each 25 mg of cortisone taken, 20 mg of hydrocortisone was substituted.

As soon as it became apparent that symptoms remained under control, the maintenance dose of hydrocortisone was gradually reduced until a relapse threatened. It was then increased slightly. The range of the maintenance dose was 20 to 60 mg per day with the majority of adults

at 40 mg and the children at 20 mg. These values vary from 40 to 60 per cent of the maintenance dose of cortisone. For the patient with chronic allergic disease, hydrocortisone appears to be roughly twice as effective, weight for weight, as cortisone.

Routine Allergic Treatment.—Desensitization was continued in all patients previously receiving such treatment and, as before, each patient was allowed to use his customary palliative medication if he felt the need for it.

Results.—All patients who had been doing well on cortisone did as well or better on hydrocortisone. Their responses can be arranged as follows:

1. *Excellent:* Two patients who had been entirely symptom free on cortisone remained so on hydrocortisone. Four who had been classified "good" on cortisone became completely symptom free on hydrocortisone. These six patients represent 27 per cent of the group.
2. *Good:* Fourteen patients (64 per cent) had good relief, in that they were symptom free for long intervals and had only mild relapses. Ten of this group had been equally good on cortisone; the other four were advanced from "fair" to "good" relief.
3. *Fair:* Two patients (9 per cent), who had only fair relief of symptoms on cortisone, continued to have the same amount of difficulty on hydrocortisone. It must be remembered, however, that in accordance with our plan all transition cases were maintained on relatively smaller doses of hydrocortisone than cortisone.

Since none of the patients who had done poorly on cortisone was transferred to hydrocortisone, it is not possible for us to compare the two steroids on the poorly reacting group.

Complications.—There were three instances of moon face and one of edema initially, but these disappeared as the hydrocortisone dosage was reduced below 60 mg a day.

The usual fluctuations in blood pressure occurred, but there was no further rise above the cortisone levels. Further weight gain did not take place or proceeded at an exceedingly slow rate. All but three of the patients felt better on hydrocortisone and were maintained satisfactorily on a lower relative dosage, thus further reducing the tendency toward side reactions. These patients represent a group maintained on steroid hormone therapy for from thirteen to twenty-eight months.

HYDROCORTISONE GROUP

Twenty patients suffering from chronic asthma who had not been on cortisone previously were placed on continuous hydrocortisone treatment. Ten of these received no adjuvant therapy except a restriction on extra

salt in the diet. The remainder were cautioned on salt and given potassium salts by mouth in amounts ranging from 1 to 3 gm daily during the initial stages while hydrocortisone dosage was 80 mg or more a day. When the steroid was reduced below this amount potassium was discontinued.

Because of the onset of pain suggesting duodenal ulcer, two patients were later put on Prantal 100 mg three times a day with control of pain.

As in the previous groups, the chief complaint of asthma had been present for more than two years in each case, and routine treatment had been ineffective in controlling symptoms. Fourteen of the patients were adults, and six were children under twelve years of age.

In this group the following were checked at regular intervals: weight, blood pressure, edema, moon face, chest x-ray and blood picture. Because there had been no changes previously with cortisone and hydrocortisone, protein bound iodine measurements were not taken.

Hydrocortisone Dosage.—As experience had shown that good results could be obtained rather rapidly with both cortisone and hydrocortisone, it was decided to shorten the initial period of full dosage of hydrocortisone and reach a maintenance dose in shorter time. This would have the double benefit of saving on the drug and avoiding the complications of prolonged high dosage.

Accordingly the following schedule was used for adults: 200 mg daily for four days, then 120 mg for three days, then 80 mg for three to seven days, and 60 mg daily thereafter for the remainder of two weeks. Subsequently the dosage was reduced gradually to a maintenance level that produced satisfactory control of symptoms. Two patients only required 60 mg per day. The remainder did well between 20 and 40 mg per day.

Children were started on 80 to 120 mg per day, depending on age, and reduced proportionately at the same rate. Their maintenance dose ranged from 20 to 30 mg a day.

Results.—

1. *Excellent:* Seven patients (35 per cent) were completely symptom free without the use of other medication.

2. *Good:* Eight patients (40 per cent) were symptom free except for occasional relapses, brought on by infection, overexertion, or unusual exposure to allergens. As in the cortisone cases, relapses responded to temporary increase in hydrocortisone or to antibiotics when indicated.

3. *Fair:* Five patients (25 per cent) obtained fair relief, in that they used small amounts of symptomatic medication several times a week, and usually showed minimal evidence of asthma.

Complications.—Three patients showed early transient mooning of the face and two had clinical edema at the start of treatment. There were

no significant changes in blood pressure, nor any of the other complications discussed under cortisone, except duodenal ulcer. One patient complained of typical ulcer pain which appeared after six weeks of treatment. Another patient was shown by x-ray to have a small duodenal ulcer after two months of treatment. Both cases responded to diet control and Prantal in full doses.

A gain in weight was noted in the majority of patients, ranging from a few pounds to 23 per cent of initial weight in one adult woman. Children showed a more pronounced gain; in six months time one gained 15 per cent, two 20 per cent, one 22 per cent and one 30 per cent of initial weights. Increased food intake appeared responsible for these gains.

DISCUSSION

The data on cortisone indicates that the undesirable side effects which would be expected at the levels of drug used can be minimized if not actually prevented by the concomitant use of adjuvants. It is true that a rather pronounced gain in weight took place, but this was attributed to an increase in appetite and sense of well-being and is not strictly a side effect of the steroid.

At the lower maintenance doses of cortisone (below 75 mg per day) adjuvants may not have been essential, although no control study was made. The fact that we were able to keep our patients for months on doses of cortisone known to produce hyperadrenalism otherwise established to our way of thinking the value of this type of symptom control.

Hydrocortisone in doses adequate to control asthma does not produce as strongly the side effects of cortisone.[3,22] In this series of cases, high doses of hydrocortisone were not used for very long, which may in part account for the low incidence of undesirable symptoms. However, a few patients did show edema and two showed activation of peptic ulcer. We believe it safer to use adjuvants whenever it is necessary to give prolonged treatment with large doses of hydrocortisone.

A comparison of the results obtained with the two steroids is shown in Table II. Hydrocortisone showed a higher percentage of complete control of symptoms than cortisone and there were no failures. The figures for cortisone and hydrocortisone respectively were: good to excellent relief, 65 and 75 per cent; or fair to excellent, 90 and 100 per cent. Too close a comparison is not justified with the numbers of patients tested, but it is safe to conclude that hydrocortisone produces better control at considerably lower relative doses than cortisone, as the average daily maintenance dose of the former was 30 mg and the latter 75 mg. These figures are in line with the results reported by other investigators.[3,22]

We agree with Bickerman and Barach that "some form of maintenance therapy appears desirable in order that the effect of a period of prolonged

TABLE II. RESULTS OF CONTINUOUS STEROID HORMONE TREATMENT OF CHRONIC ASTHMA AND NEURODERMATITIS WITH CORTISONE AND HYDROCORTISONE

Patient Group	Results of Treatment							
	Excellent		Good		Fair		Poor	
	No.	%	No.	%	No.	%	No.	%
Cortisone 32 cases	3	9	18	56	8	25	3	9
Transition 22 cases	6	27	14	64	2	9	0	0
Hydrocortisone 20 cases	7	35	8	40	5	25	0	0

improvement in the activity of the disease process could be evaluated."[3] While it is too early to be definitely stated, it is our impression that prolonged control of symptoms in chronic asthma does not "cure" the disease except in a small fraction of cases. Relapses take place even after two years of cortisone and hydrocortisone treatment. These patients need treatment indefinitely, and the development of more specific steroids such as prednisone and prednisolone is highly desirable.

Finally, it must be noted that adrenal steroid therapy at acceptable levels with presently available compounds does not produce complete control in the majority of chronic allergic patients. It is still necessary to use to the fullest extent the other accepted methods of treatment.

CONCLUSIONS

1. Long-term steroid hormone therapy can be expected to produce substantial relief when used in otherwise inadequately controlled asthma and neurodermatitis.
2. Relatively high doses of these hormones do not necessarily produce undesirable physiologic side effects provided suitable adjuvant therapy is given at the same time.
3. Adjuvants found most useful were low salt diet, oral potassium salts, anticholinergics, estrogens and androgens.
4. On cortisone 65 per cent of thirty-two cases showed from good to excellent relief, and 25 per cent showed fair relief.
5. On hydrocortisone 75 per cent of twenty cases showed from good to excellent relief, and 25 per cent showed fair relief.
6. Lower maintenance doses of hydrocortisone can be given with minimum use of adjuvant therapy.
7. Treatment for months or years of chronic allergic disease by means of relatively small amounts of cortisone or hydrocortisone is entirely feasible, but other methods of control are still required.

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Submitted October 17, 1955

EVALUATION OF ISUPREL-FRANOL® IN THE TREATMENT OF THE ASTHMATIC ATTACK

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THE purpose of this study was to ascertain the ability of a combined sublingual and oral tablet to control severe individual attacks of bronchial asthma and maintain this relief for periods of several hours or more in the chronic type of severe asthma.

Effective means of relief for the acute asthmatic attack already exists in the usual adrenalin hydrochloride 1:1000 injection or in the various epinephrine 1:100 oral sprays. Similarly effective is the sublingual administration of isopropylarterenol hydrochloride. However, frequently such measures give immediate but only short relief with recurrence of the asthmatic attack and need for again using such medication.

Arthur G. Baker[1] reports a successful attempt at potentiating the effect of sublingual isopropylarterenol by combining it with benzyl nicotinamide. He reports patients were relieved in 85 per cent of the asthmatic attacks after using this potentiated tablet; that the relief came in ten minutes and lasted three to four hours.

This present report similarly deals with a potentiated sublingual Isuprel-Franol®* tablet. This is a tablet whose very soluble outer coating contains 10 mg of Isuprel (isopropylarterenol hydrochloride) and whose core consists of benzylephedrine 30 mg, Luminal® 8 mg, and Theocin® brand of theophylline 120 mg. The patient is instructed to place the tablet sublingually and to wait until the lemon taste of the isopropylarterenol hydrochloride has disappeared and then swallow the remainder of the tablet.

PHARMACOLOGY

Isopropylarterenol hydrochloride has previously been shown by Lipman[3] to be effective by subcutaneous injection, by the oral route, by aerosol, and by sublingual administration, and has been shown to control experimental asthma induced by choline aerosols and pilocarpine-induced bronchospasm. He reports that eleven patients in the adrenalin-fast state responded favorably with this drug.

There is evidence to show that the systemic administration of isopropylarterenol hydrochloride gives the best results. Leon Cander and J. H. Comroe, Jr.,[2] point out the disadvantages of aerosolized bronchodilators, namely, that they probably exert their effect only on patent airways or on partially obstructed airways and are unable to reach completely occluded areas of the lungs. On the other hand, drugs administered systemically

*Isuprel-Franol, Winthrop Laboratories, Inc., New York.

reach all bronchioles, whether obstructed or patent, by way of the pulmonary circulation.

Franol, the second part of the compound being studied, has been added as a potentiator of the isopropylarterenol effect. J. A. Rudolph[4] previously studied this medication separately, and found 85 per cent of the sixty asthmatic patients treated with it over a period of from three to six months were greatly benefited. The average number of tablets taken varied from three to twenty in a twenty-four-hour period. It was found to be without side effects in 94 per cent of the patients treated and definitely effective in relieving mild to moderately severe paroxysms of asthma.

Thus by combining Franol with Isuprel, we had a combination of drugs which pharmacologically could be effective in giving immediate relief for the individual asthmatic attack and continued relief for the patient with chronic asthma.

SELECTION OF PATIENTS

All patients accepted for treatment had severe asthma. All individual asthmatic attacks so treated were to be severe and of the type requiring adrenalin hypodermically or by inhalation for relief. In all, twenty-five patients were treated. They were divided into two groups, as follows:

Group A consisted of fifteen patients, ranging in age from nine to sixty-five and including eight males and seven females, who on two or more occasions were treated for individual acute attacks of severe asthma.

Group B was made up of ten patients, equally divided as to sex and ranging in age from thirty to sixty-four, all of whom had chronic severe asthma and who were treated continuously for a period of from one to twelve months.

RESULTS

In Group A, twelve of the fifteen patients showed marked relief on one tablet in five minutes, one fair relief in five minutes, and two no relief. Eight of these fifteen patients were completely relieved of their asthma after twenty minutes, and four patients were 75 per cent relieved after a similar period. In three patients the effect after twenty minutes was considered unsatisfactory.

In Group B, nine out of the ten patients obtained satisfactory relief of their chronic asthma on this type of medication. Four of these patients had been treated for twelve months, one for seven months, one for three months, and four for one month. All had previously been on other remedies for relief of their asthma, including ephedrine compounds and aerosol 1:100 epinephrine.

Four of the nine patients successfully treated had previously been adrenaline-fast. On two occasions two of them demonstrated the development of Isuprel-Franol-fastness.

The average twenty-four-hour dose required for satisfactory relief of their chronic asthma was two to three tablets.

SIDE EFFECTS

In Group A, three of the fifteen patients developed a feeling of apprehensiveness and were conscious of an increased heart rate within five minutes after being given the medication.

In Group B, two patients had to discontinue the medication because of the development of persistent tachycardia and apprehensiveness.

SUMMARY AND CONCLUSIONS

1. Isuprel-Franol is definitely effective in relieving both severe acute individual attacks of bronchial asthma and in relieving chronic asthma.

2. This combination offers complete to moderate relief in the acute individual attack of asthma, and it also maintains this relief in 80 per cent of the patients.

3. It has been extremely effective in nine out of ten patients treated with chronic asthma.

4. It has been found effective in four patients with adrenalin-fastness, and in only two out of the twenty-five patients treated was fastness to this new combination of drugs noted.

5. The only side effects noted were apprehensiveness and tachycardia, occurring in 20 per cent of the acute as well as the chronic cases. In two of the twenty-five patients, the medication had to be discontinued because of these side effects.

6. This drug combination has proved helpful in the treatment of patients with asthma, but its use should be in association with the usual specific allergic treatment of these patients.

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141 East 56th Street
Submitted November 21, 1955

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HAY FEVER OR POLLEN POISONING

Historical Document

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About sixty years ago (1819), Dr. John Bostock, of London, described as an unknown disease, "A Case of Periodical Affection of the Eyes and Chest," which was marked by the following characteristics: an acute catarrhal inflammation of the mucous membrane of the eyes and air passages, accompanied by asthma, recurring regularly during the early Summer of every year, lasting several weeks, and resisting all therapeutical treatment. On further investigation, Dr. Bostock found that the disease was not extremely rare, but was known to the laity, if not to the profession, and had by them been attributed to newly-mown hay as a cause, and consequently called "Hay Asthma" and "Hay Fever." Soon after, Mr. Gordon published a case with remarks as to its origin, and subsequently Dr. Elliotson and Sir Thomas Watson described it in their lecture courses, and the republication in 1843 of Watson's lectures, soon spread a knowledge of the disease through the profession. Since then it has been described in most of the text-books on Diseases of the Chest, several books have been devoted to it, and numerous articles have been contributed to the periodicals. The most important of these European works are those of Phoebus and Blackley.

A similar form of disease has been observed in this country for many years, but the first notice of it in any medical work, occurs in the "Treatise on Diseases of the Chest," by Dr. J. A. Swett, of New York, published in 1852. He writes, "New-mown hay in some persons will induce an attack (of bronchitis), often attended with marked dyspnoea. The flowering of roses in some persons will spoil the month of June, and I have seen individuals who habitually lose the enjoyment of our fine Autumn from similar attacks, but what particular cause I have not been able to ascertain." It thus appears that Dr. Swett recognized two varieties of periodical catarrh—one occurring in June and the other in the Autumn. In 1854, Dr. Morrill Wyman described the disease in his lectures at the Medical School of Harvard University. In 1856, Dr. G. A. Kinkler, of Madison, Ind., published a report of a case of periodical catarrh, and in 1861 Dr. James Darrach, of Philadelphia, published three cases. In 1866 Dr. Wyman read a paper on the late form of Hay Fever, at the meeting of the Massachusetts Medical Society, and gave it the name of "Autumnal Catarrh"; and at the same date Dr. T. T. Price, of Tuckerton, published an article on the same subject, calling the disease by the same name, in the

Essay read before the New Jersey State Medical Society and published in its transactions in 1877.

Transactions of the Medical Society of this State. In 1872 Dr. Wyman published an exhaustive and valuable work on "Autumnal Catarrh," drawn from a large experience, which materially increased our knowledge of the disease, especially in regard to its causes and geographical distribution. Dr. G. M. Beard, of New York, also published a work on "Hay Fever," in 1876, which contains some interesting information.

Of the two American forms of the disease, that occurring in June and that in September, the latter is by far the more frequent. It is this form which is usually meant when Hay Fever is spoken of, and which is the subject of this essay.

The disease consists of an acute inflammation of the mucous membrane of the eyes and air passages, varying greatly in severity and in extent of tissue involved. The eyes and nose alone may be affected, or it may spread deep into the bronchial tubes. The symptoms are such as might be expected from this condition. They commence by a feeling of irritation in the eyes and nose, lachrymation, sneezing, stuffing up of the nostrils, and great itching of the parts; the eyelids and nose become red and swollen, and there is a profuse discharge of serum. This state lasts for a few days or a week, when a dry cough and some dyspnoea set in, and these may be of any degree of intensity, from a slight embarrassment of respiration on exertion to the severest form of spasmodic asthma. These symptoms continue with occasional short periods of alleviation and exacerbation for about six to eight weeks, and then subside, and the patient regains his health until another year comes round. During the course of the disease, the general system will be affected in proportion to the severity of the local inflammation and the strength and nervous irritability of the patient. There is seldom headache, feverishness or affection of the digestive organs. The distinguishing characteristics of the disease are its annual recurrence at the same season of the year, its defined period of both commencement and termination, and its incurability. The season of attack is from the middle of August to the beginning of October, with slight variations of both duration and intensity in different years.

The disease may make its first appearance at any age from early childhood to above fifty years. . . . When once it appears, its recurrence has never been known to cease. It is often hereditary, and runs in families. Dr. Elliotson observed this peculiarity in some of the few cases which fell under his notice, and subsequent observations have confirmed his opinion, so that heredity is now one of the recognized characteristics of the disease. It is found more frequently among males than females. . . .

When Dr. Bostock first investigated the disease, he found that the public had named it "Hay Asthma," and ascribed it to the influence of newly-mown hay. After conscientious observation, he could trace no such relationship of cause and effect in his own person, and considered the influence of Summer heat as far more important. Mr. Gordon's observations led him to the opposite opinion: he found that persons subject to the

disease could not approach meadow fields without bringing on an aggravation of their sufferings, and also noticing the particular season of attack, drew a conclusion that it was caused by flowering grasses, and gave as one reason "because as it (the grass) begins to flower and *not till then,* the asthma commences; as the flowers arrive at perfection the disease increases, and after they have died away patients can pass through the most luxuriant meadow with total impunity." Dr. Elliotson adopted this view, and suggested that the pollen of the grass might be the active principle. This opinion was the prevalent one for many years, and the disease was ascribed to some influence connected with vegetation. It was not, however, undisputed, and other causes were still suggested. . . .

In 1873, Mr. Charles H. Blackley, of Manchester, published a work on Hay Fever, giving a series of most valuable experimental researches on many of these supposed causes, and established conclusively the fact that the pollen of several plants, especially the grasses and cereals, is the real cause of the Summer Catarrh as it exists in England. . . .

He first showed that many of the supposed causes, especially heat, light, ozone, strong perfumes, dust, are entirely insufficient to account for the disease. He then experimented carefully with the pollen of various flowers, by applying it to the mucous membrane of the eyes and nose, and causing it to be inhaled. He applied the pollen in a fresh and dry state, and also in some cases prepared an alcoholic extract. The experiments were made chiefly upon himself, but also upon others, subject and not subject to the disease. The pollen of most grasses and cereals, when applied to persons, subjects of Hay Fever, was found to have an irritant effect, and to produce symptoms precisely similar to those of Hay Fever. . . . The pollen of Secale Cornutum (rye) was taken fresh from the plant and applied to one nostril; "A profuse coryza came on in less than a minute after the application. In thirty minutes the nostril was completely occluded, so that it was quite impossible to pass any air through it. During the day the sneezing and the coryza kept up at intervals, and lasted for six or eight hours." In some instances where the pollen was inhaled, decided asthma supervened. The pollen of various grasses and flowers was tried with varying results, some producing no symptoms, and some being as irritating as that above described. "The action of the pollen of the order Graminaciae was on the whole very distinct and well marked. The quantity and irritating power of the pollen was not always the same. It varied with the season, as this was dry or wet, warm or cool, early or late in flowering, and other circumstances."

Having thus ascertained the irritant properties of pollen, Mr. Blackley undertook a series of experiments to find out the quantity that might be floating in the atmosphere and carried about by the winds. . . . The experiments are numerous, ingenious, careful and convincing, and completely establish two points: 1st, That the pollen of grasses, applied to the mucous membrane, produces all the symptoms characteristic of Hay Fever. 2d,

That it is present through the atmosphere in large quantities during the season of Hay Fever in England, and during this season only. Mr. Blackley concludes that these observations prove pollen to be the cause of Hay Fever, and suggests that it should rather be called "Pollen Catarrh," or "Pollen Asthma."

In this country, too . . . . a general opinion prevailed that the periodical catarrhs were in some manner dependent upon vegetation, and the English name of Hay Fever was retained. The early form was by some persons attributed to blossoming roses, while the more common September variety was ascribed to various plants flowering at that season; and Indian corn, Golden Rod, Roman wormwood or Ragweed, have each been selected as the offending cause. This opinion, however, was by no means universal. Many regarded it solely as a personal idiosyncrasy, arising from some unknown peculiarity or some perhaps derived a melancholy satisfaction from being thus the subjects of a mystery, and carefully noted every symptom and every deviation from health as being in some way connected with their peculiar constitution. Those who adopted the former view did not deny the existence of a peculiarity of constitution, but only attempted to find a cause competent to produce such symptoms in the susceptible individuals.

The writer has been a sufferer from this disease since childhood, and has had it in all grades of severity, from a troublesome coryza to spasmodic asthma, relieved only by chloroform. For many years he was unable to ascertain or even suspect any special cause, although he believed it to be in some way connected with vegetation. In 1865 his disease had been arrested by a sea voyage, and subsequently by a visit to the Isles of Shoals. About 1870 he had his attention called to the Ragweed as a possible cause of the disease, although previously he had not even known the weed by name. This plant is the Ambrosia artemisiaefolia, called Roman wormwood, ragweed, hogweed; it grows along all roadsides, waste and neglected places, and begins to bloom about the middle of August, the blossoms being small and insignificant, but producing an extremely abundant fine yellow pollen.

In 1866, Dr. Price had confidently suggested that the cause of Autumn Catarrh would be found in the pollen of some of the numerous plants of the order Compositae, which come into blossom in August and September. . . .

I have noticed the extreme abundance and wide diffusion of the ambrosia during my travels to escape it. In this section of the country it may be said to grow everywhere. Roadsides, stubble fields, waste places, everywhere abound with it, and few of the most highly cultivated gardens are free from it. It is only after the attention has been directed to the plant that its universal presence is observed. It seems to spring up by magic everywhere. . . .

I have observed the course of the disease has been directly affected by the character of the season and the amount of ambrosia springing up. For

instance, in 1875 the ambrosia was very forward in season and abundant in quantity. Severe symptoms came on early, and those who remained at home suffered more than usual. In 1876, owing perhaps to the extreme heat and drought, there was not one quarter the amount of ambrosia as in the previous year, so that I myself was able to remain at home with comfort a week later than my usual time, and the season was generally found a mild one for Hay Fever subjects.

I have also carefully watched for the first blossoming of the ragweed, and have noticed that the earliest catarrhal symptoms never come on previous, but always succeeding to that event.

On August 5th, 1874, I picked a few racemes of ambrosia, the flowers of which were in full bud but not quite opened, and placed them in a glass of water in my office. This hastened the ripening so that on the next day they scattered pollen abundantly on handling them carelessly in the preparation of some specimens for the microscope. For twenty-four hours afterwards I suffered from a severe coryza, with occlusion of the nostrils and serous discharge. The symptoms then passed off, and I had no recurrence of them until August 13th, when I repeated the experiment and also applied some of the pollen directly to the nostrils. This produced immediately such severe catarrhal symptoms, that the next day I took a hypodermic injection of morphine for their relief. The symptoms did not pass off but continued into the regular attack which should have commenced a few days later. A friend, not subject to the disease, at the same time tried the same experiment and was entirely unaffected. . . .

In 1875 and 1876 I made some experiments on the presence of pollen in the atmosphere. . . . In 1875 my friend continued the observations on the slides in the suburbs of the town, with the constant result of finding ambrosia pollen deposited daily and in large quantity. The following are specimens of his observations:

August	28th,	one	day's	exposure	80	grains
"	29th,	"	"	"	51	"
Sept.	2nd,	"	"	"	4	"
"	3rd,	"	"	"	112	"
"	4th,	"	"	"	204	"
"	5th,	"	"	"	310	"

He also wrote to me as follows: "On September 10th I cut a couple of slides of glass, put some gum and glycerine on them, placed them together and enclosed them to - - - , with the request to place them on one of the attic window sills of his house, (Twelfth Street, New York) expose them for two days, then place them together again and return them to me. I found plenty of ragweed pollen on them, and counted 30 grains in about a square centimetre. On September 8th, I placed a slip on the roof of our own house, exposed it horizontally for nine hours, and found 49 grains on it,—the same day the slip on the lawn contained 310 grains." In the

summer of 1876, Dr. B. A. Segur, at my request, made a number of similar observations in the city of Brooklyn, and found ambrosia pollen constantly, though not in large quantity, on the slides.

From these investigations the writer has formed the opinion that Autumnal Catarrh, like the English form of Hay Fever, is caused by the presence of pollen of flowering plants in the atmosphere, and its irritant action on the respiratory mucous membrane of susceptible persons, and that the pollen of the ambrosia artemisiaefolia permeates the atmosphere during the continuance of the disease, and is capable of producing all the usual symptoms. He believes that it is probably the only cause, although it is not impossible that the pollen of other plants may be equally irritant, and produce the same effect when present in sufficient quantity. . . .

The arguments in favor of the view that Autumnal Catarrh is caused by the poisonous influence of the pollen of ambrosia and other plants may be briefly summarized as follows:

1st. Blackley's experiment proves the irritant properties of the pollen of grasses, its great prevalence in the atmosphere and its agency in the production of the English form of Hay Fever.

2d. Dr. Wyman's and the writer's experiments show the same qualities and prevalence of the pollen of the ambrosia.

3d. The commencement, course and termination of the disease coincide precisely with the blossoming of the ambrosia.

4th. Numerous observations have shown the coincidence of the beginning of an attack or of paroxysms of the disease with exposure to the direct influence of ambrosia.

5th. The chorographic relations of the disease. The existence of catarrhal and non-catarrhal regions as laid down on a map with no apparent reference to the climate, temperature, elevation or other physical qualities, appears to indicate some local cause for the disease. . . .

6th. The insufficiency of all other assigned causes. It is unnecessary to state in full the various facts and observations relating to the causes frequently assigned, such as summer heat, bright light, presence of ozone and electricity, depression of the nervous system. . . .

7th. Hay Fever is a local and not a constitutional disease. In one sense there is something more than the local trouble; there is a peculiar sensitiveness to the exciting cause, existing only in exceptional instances. We call it an idiosyncrasy, but as yet we know nothing of its nature or cause. . . .

The objections brought against the pollen theory are as follows:

1st. That some of the symptoms and circumstances of Hay Fever indicate a general and not a local disease. Especial stress is laid on the idiosyncrasy as the chief agent in the production of the disease, and on the influence of inheritance and occupation. These influences cannot be disputed, but, as has been shown, they cannot be regarded a sufficient cause for the disease. . . .

The incurability of the disease is supposed to indicate its constitutional nature. "It cannot be controlled locally, and its very intractability under such medical treatment as that to which ordinary catarrh, in its first stages especially, not infrequently yields, points to something deeper and more radical than can be supposed of a trouble merely local." So far from this intractability *to medicine* proving Hay Fever to be more than local, its very tractability to *appropriate treatment* should prove the reverse. Could any physician expect to cure a local disease, the cause of which was constantly present and acting. If a person were living in a room the atmosphere of which was filled with smoke or a fine powder of pepper, could he expect any amount of lotions, douches, or drugs to prevent lachrymation, sneezing, and severe irritation of the mucous membrane; but on the other hand, if appropriate treatment be used, if he be removed from the impure to a pure atmosphere, the trouble will soon subside. And the same is the case with Autumnal Catarrh.

3d. Perhaps the strongest argument against the efficacy of the pollen of ambrosia to produce Autumnal Catarrh, is based on certain experiments of Dr. Wyman . . . who holds the view that ambrosia "can be regarded as only a very active and general cause of paroxysms, not a cause of the whole disease," [and] is inclined to believe . . . that it may vary in its properties when growing in different regions, and that it possesses irritant power in the "critical period" only. There are reasons to believe that this is true, especially since the researches of Mr. Blackley have shown that there is considerable variation in the activity of other kinds of pollen, dependent upon the character of the season and the period of ripening. Among other modifying circumstances he found that when ripened prematurely, or when used dry instead of fresh, only a minimum effect was produced by the pollen. . . .

The remedies suggested and tried for the cure of Autumnal Catarrh are numerous, and although many have been vaunted as specifics, none have stood the test of time and experience. Most sufferers from the disease have gone through a long list of medicines, one after another, with little benefit, but yet they look hopefully and eagerly for every new suggestion. Quinine, iron, arsenic, ammonia, camphor and carbolic acid,—each has had its advocate,—and still the disease makes its annual visitations and goes on with unimpeded progress. After fifty years' investigation we have not advanced beyond Dr. Bostock, who said: "The experience of many years has taught me not to expect a cure for the complaint, and I now only aim at relieving any peculiarly urgent or distressing symptoms"; and he gives a list of the remedies which he has tried without success, in order to prevent others from making similar experiments. There are a number of remedies which may be used to alleviate the sufferings from the disease, and after a long experience the writer would select the following as affording most comfort, and being most generally useful: the hypodermic injection of morphine, cold water and simple cerate for the eyes and nose,

Espic's cigarettes for the cough, and chloroform for the asthma. Morphine, administered hypodermically, will give most decided relief in many cases. It is useful in all stages and degrees of the disease; it appears to diminish the congestion and serous secretion of the membrane, relax bronchial spasms, and allay nervous irritation. Its use was first recommended by Dr. Wm. Moss, of Philadelphia, in the *American Journal of Medical Sciences,* January, 1873, and the writer has since used it with decided benefit.

But although we have not advanced beyond Dr. Bostock, in finding any specific remedy for the disease in our Materia Medica, we have been more fortunate in finding a cure by other means. We have ascertained that there are certain regions of the country which are exempt from Autumnal Catarrh, and that a temporary residence in these places will procure exemption or effect a cure. Much credit is due to Dr. Wyman for his study of these chorographic relations of the disease, and although the boundaries between the catarrhal and non-catarrhal regions are still imperfectly defined, yet he has been a benefactor to many sufferers by pointing out this source of relief. It is unnecessary here to name these exempt regions. They are marked on the maps in Dr. Wyman's book, and are now generally known through the community.

When sufferers from Hay Fever find that no cure is known except banishment from home, the following question presents itself: Is it not probable that some cure can be found? Must we continue to suffer yearly from these attacks? No positive answer can be given to these questions. There is no reason why some remedy may not be found to modify the peculiar susceptibility, or to neutralize the effect of the irritant; but the writer is not at all sanguine of any success in such attempts; he is not aware that success has been attained in the destruction of any other idiosyncrasy. . . . Possibly a respirator may be invented which can be worn with comfort, and yet prove efficient in protecting the sensitive mucous membrane from the pollen. Perhaps nature, who caused the idiosyncrasy, may remove it; but her ways are inscrutable. . . . Naturalists know that a change in the character of vegetation is constantly going on. In the struggle for existence some plants disappear and others take their places. Sometimes insects or parasites destroy them utterly. Peach and plum trees have almost disappeared from some sections of the country where they were once abundant. The grape vines of Madeira and southern France have been destroyed, and recently the potato vine has had and is having a hard struggle for life. If these things have happened notwithstanding the aid of man's interest in their preservation, why may we not hope for the destruction of a noxious weed! This may appear to many as a distant comfort, but the writer has none other to offer.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PROPERDIN

From the studies on the mechanisms of complement action conducted in the laboratory of Louis Pillemer at Western Reserve University over a number of years evolved the discovery of an additional component in the serum of human being and other mammals, which seems to be implicated in nonspecific resistance to infection and shock. This proteinic material, called properdin by Pillemer, was recognized by its ability to form a complex with zymosan, which inactivates the third component of complement. All four components of complement, however, are necessary for its activity, and so are magnesium ions. Properdin behaves like a complex euglobin, comprising, as such, a small fraction of the total serum proteins (about 0.02 per cent).

The properdin complex (= properdin + complement + Mg) is necessary for the bacterial action of normal serum on a variety of bacteria and the inactivation of several viruses. It is also involved in the lysis of abnormal erythrocytes and the killing of certain protozoa, for instance, *Toxoplasma.* Properdin itself is consumed during these reactions, but complement, though necessary for properdin action, does not diminish measurably. Strangely enough, not all strains of a given bacterial species are equally sensitive to the killing effect of the properdin system. At least for several *Enterobacteriaceae* it has become known that there may be sensitive, partially sensitive and nonsensitive strains in the same species.

Little is known yet about the *in vivo* action of the properdin system. No primary deficiency is known. Low titers of properdin were observed in animals after infection, shock and exposure to radiation. Similar findings were obtained during bacterial infections in human beings. These observations are in agreement with data, according to which properdin combines *in vitro* with other polysaccharidic components of microbial cell walls beside zymosan. On the other hand, an increased properdin titer was recorded in human beings after the administration of minute amounts of the purified polysaccharide complex from typhoid bacilli. Low properdin levels were found in a case of paroxysmal nocturnal hemoglobinuria, the one disease where a relationship of properdin with hemolysis had been demonstrated.

(Continued on page 226)

Progress in Allergy

THE REPORTING OF DRUG TOXICITY

Part I

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PHYSICIANS are frequently urged carefully to weigh the advantages and disadvantages of drugs; to prescribe them with care; to administer them only when they are actually indicated and then, when no other equally effective but potentially less hazardous agents are available. Exemplifying this attitude is the exhortation,[47] "Modern drug therapy requires all interested parties to be properly informed and to meet their responsibilities . . . (the physician) . . . should ask himself if another equally effective but potentially less hazardous drug is available; if not, he should ask whether the advantages outweigh the disadvantages." Or again, physicians are told,[66] "It is obvious that we owe it to our patients to use new drugs whenever the dangers of the disease outweigh the dangers of the drugs. In so doing we must know both the merits and dangers of the drugs." And again, physicians are alerted[40] that, "The final decision" (between the dangers of withholding treatment and potential toxicity of the drug) "is one for individual judgment to determine . . . the important thing is, that the arbiter, of the decision, be aware of the problems involved and the dangers implicit in either cause of action." It is said,[58] "Each day every practicing physician or surgeon must use his best judgment . . . and[28] must employ them (the drugs) wisely and with the fullest advantage of current research."

How well equipped is the physician to comply with this sound advice? He must, of course, keep informed of the recent literature concerned with the reactions caused by drugs. His absolute dependence upon such reports of reactions necessitates a critical examination of their nature and adequacy. But, with our present method of reporting toxicity, the clinician faced with a particular patient has neither the information nor the attitude he needs to measure the hazards involved in using modern potent drugs.

The current approaches to the problem of drug reactions antedates the introduction of the sulfonamides, before the discovery of which physicians were almost entirely limited to the prescription of either nonspecific or palliative medications. In almost all cases the drugs kept our patients comfortable during the time it took for them to recover or to die. In those days it could well be said, "Primum non nocere," and "Vis Medicatrix Naturae." When drugs were prescribed for comfort, discomfort became important and minor effects of toxicity became major subjects of consideration.

The drugs we prescribe today are potentially both life saving and death dealing. Withholding the best drug available may be just as morally indefensible and, actually and scientifically, just as much the cause of

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death as prescribing the drug may be to a known allergic individual. A precise understanding of what is to be known of the reactions supposedly caused by drugs is (to repeat for emphasis) absolutely necessary.

For these and other reasons, our approach to the problem of drug reactions must be reviewed (Part I). We can then also explore the possibility of a better method of reporting the various types of untoward effects (Part II). Anything less than the most carefully thought-through reports of toxicity can either communicate an undue enthusiasm for the drug or an unwarranted fear of its use, or else a swing from one extreme to the other. Such extreme attitudes are both invalid and harmful to our patients, because a drug which has passed through the vicissitudes of optimism and pessimism rarely finds its way back to its exact place in our armamentarium. Both physician and patient are human and, unhappily as seen in medical history, drugs are consistently considered to carry reputations for good and evil, neither of which is related to the facts.

An example of the effects of such oscillating attitudes is seen in the use of penicillin. The present-day warnings against its indiscriminate use have so been taken to heart that as Smith et al[59] say, they have "induced physicians to withhold indicated treatment" with consequent effects not only on the patient involved but on the entire national venereal disease program.

Another example, classic in its confusion is the true history of Cinchophen. In 1921, case reports appeared suggesting a relationship between its use and hepatic necrosis. In 1933, Short and Bauer[57] reported on four such cases and reviewed a number of others. In 1936, Palmer and Woodall[50] had collected 191 such cases with all of eighty-eight deaths. But in 1943, when Ottenberg and Spiegel[49] had re-reviewed the evidence, they found it inconclusive. In 1947, an editorial in the *J.A.M.A.*[20] asserted that the atrophy of the liver erroneously attributed to Cinchophen administration was, in fact, infectious hepatitis. In 1955, Alexander[1] concluded, "that a drug in itself is not directly hepatoxic is fairly well established." Cited is Snyders'[60] series of 2,500 patients in which there was no case of hepatitis. In 1955, Holland,[37] the Medical Director of the FDA, used the case of Cinchophen as an example of how reactions might "erringly (be) attibuted to drug administration or to the wrong drug." Nevertheless, the 1955 edition of the most widely used textbook in pharmacology repeats all of the early history of the toxicity of Cinchophen. It does not discuss its recent exoneration. And, as in the case of Chloromycetin,® the decline in the number of fatalities is ascribed not to the true cause, the inherent safety of the drug, but to its more careful or lessened use. Any physician who has not had occasion to unravel this intricate pharmacologic story is understandably confused regarding the status of Cinchophen. He probably does not prescribe it but instead administers Colchicine, a drug which although it has truly been associated with fatal toxic reactions nevertheless enjoys a good reputation; cold comfort to the family of a patient who dies of Colchicine intoxication.

TOXICITY REPORTS

What information is available to the clinician who must prescribe any particular medicinal agent? The pertinent literature presents him with four general types of reporting: (a) Epidemiological studies of the incidence of drug reactions; (b) studies of series of patients treated with

the drug; (c) case reports of one or of a few instances of such supposed drug reactions; and (d) reviews of such case reports.

EPIDEMIOLOGIC STUDIES

The most reliable information available comes from surveys of the type written by Welch et al[68] concerned with the possible relationship of Chloromycetin and aplastic anemia. This study demonstrated that every major group of drugs, including the broad spectrum antibiotic agents, the antihistaminic agents, the sulfonamides, the barbiturates and also the salicylates might be implicated as possible causes of blood dyscrasias and of fatal hemopoietic reactions. It did not prove that Chloromycetin actually caused any of the dyscrasias described. The evidence against the other drugs and groups of drugs was equally flimsy and based only upon the validity of a *post hoc, propter hoc* relationship.

The problem involved is easily outlined but not easy to unravel.

Aplastic anemia occurs "idiopathically." Its cause is unpredictable as regards exacerbations and remissions. Aplastically anemic patients are subject to easy and frequent infection. Such infections must be treated with drugs often life saving but in themselves said to be, and often apparently capable of, causing aplastic anemia.

But, aplastic anemia may be caused by exposure to nonpharmacologic toxins as benzol and hair dyes. Again, such patients are subject to infection which again must be treated with drugs often life saving but in themselves. . . .

And yet aplastic anemia, when not idiopathic, may be caused by infections, either in a normal patient "afflicted with an overwhelming infection" or "in a person who has a congenitally hypoplastic bone marrow in whom a moderate infection may precipitate the disease" (Whitby and Britton[71]). What are the infections known to cause aplastic anemia in patients who have not been treated with the drugs in question? They are the very disorders for which the use of the drugs is mandatory. The list includes osteomyelitis, pansinusitis and lateral sinus thrombosis, Vincent's infection of the oral cavity, acute liver abscess, pneumonia, septicemia due to staphylococci, streptococci and *B. Friedlanderi*, typhus, typhoid, measles, mumps, malaria and influenza, among many others. On the subclinical level—which was first, which second? And again the infection must be treated with drugs often lifesaving but in themselves. . . .

But the drugs themselves (omitting penicillin) may cause aplastic anemia, but they are only given to infected patients who may be aplastically anemic, or who may respond to infections with aplastic anemia, or who may react to the drugs with present or future aplastic anemia (although the infection responds to the drug), or who may react with aplastic anemia to both infection and a drug, or who may react to the combined effect of the several drugs given, or not being aplastic at the time may at some future time independently become aplastically anemic. And, to add to the difficulties, the circumstances can rarely be reversed or the experiment repeated or subjected to objective proof!

That aplastic anemia occurs there is no doubt. That its incidence has not increased since the advent of the use of the antibiotic agents is equally beyond doubt. But that it is due (on the basis of ten to twenty-five cases for each broad spectrum antibiotic agent) to any one of the drugs, and especially so when several have been prescribed, is doubtful indeed. On the other hand, the evidence of dyscrasias due to the antipyrines appears

satisfactory although the incidence is low, the reasoning as sound as any medical *post hoc, propter hoc* relationship can be with some of the "one-time" case reports hardly acceptable.

Similarly, an analysis of 184 deaths due to agranulocytosis[56] in the Netherlands, during 1952-1954, lists 103 cases following the administration of such common medicinal agents as aminopyrine, sulfonamides, gold salts, phenobarbital, irgopyrine, peroxide, acetylsalicylic acid, phenacetin, diparcol, optalidon, uracil preparations, sanalgin, antipyrin, globenal and salvarsan.

In this context, Holland *(op. cit.)* says, "At any one time a given bio-system or series of bio-systems may inexplicably fail to respond as predicted or may respond in a hypersensitive or idiosnycratic or other adverse fashion. At best, then, we are dealing with biostatistics in which probability must play a major role . . ."

Only by several large scale series of unselected cases or by statistically structured sample studies can we find any clue as to the frequency with which hypersensitivity reactions may be expected to occur. In this respect, individual case reports misinform us to the extent that it is a matter of chance as to whether they happen to be submitted for publication, and, if so, whether they are printed. This type of reporting compounds chance with chance.

Thus, on the basis of the Food and Drug Administration survey[70] of acute anaphylactoid reactions to penicillin and other antibiotic agents, it was estimated that annually there are from 100 to 200 such reactions, of which 30 per cent are fatal. This survey, however, elicited the fact that of the eighty-four such cases disclosed, twenty-four of them fatal, none had *ever* been reported.

Valuable though these studies may be, they are not clinically significant unless or until the physician has statistical data on the number of patients *exposed* to the drug. He needs to know the incidence of blood dyscrasias or other syndromes similarly attributed to the drug in the population at large not so exposed. Thus, Haviland[33] has reported that the incidence of aplastic anemia in the general population is greater than the incidence reported as following Chloromycetin administration, a fact which challenges the popular impression that the drug may cause a blood dyscrasia.

Unfortunately, the number of patients who have been exposed to any one drug is not generally available. The most likely source of such information is the drug manufacturer himself. But if he knows, the numbers are not released except in the few instances when they are revealed as a purely defensive measure. Thus, when the criticisms of Chloromycetin were published, Parke Davis & Company made known for the first time that at least 8,000,000 patients had then (1954) been treated with it. They placed the reports in their true perspective. We know, in the same way, that by late 1955, 42,000,000 doses of ACTH had been administered, in some cases over a period of sixty-six months, and that 4,000,000 people had been exposed to chlorpromazine. Similarly, when a report was published on a series of fatalities allegedly following the administration of Butazolidin,® the manufacturer estimated that approximately 3,000,000 patients in the United States alone had taken the medicinal agent. If all the cases implicating the drug had been proven to be valid, the incidence of serious reactions remains lower than that for alternative drugs and for some drugs lower than the incidence of dyscrasias alone for the general population.

STUDIES OF SERIES OF PATIENTS

How valuable is a study on the incidence of reactions in a large series of patients? The question is essentially one of statistical validity. The incidence of serious reactions to drugs prescribed frequently is, at most, very low. If this were not true, the drug would both quickly fall into disfavor with physicians and rapidly be withdrawn.

In the incidence of blood dyscrasias, for example, we are dealing with statistical quantities of the order of magnitude of say, 1:100,000 to 1:500,000, or less. When the incidence is so low, it is a matter of pure chance whether, in a series of 2,500 or 5,000 patients, there are no or a few cases of blood dyscrasias. The observer who met none in his first 2,500 might by chance see five in his next consecutive 2,500 patients. Conversely, a worker who reported five cases in 2,500 patients might well encounter none in a succeeding 2,500. These issues of probability and of statistical validity are the reasons for conflicting reports of the incidence of serious toxic reactions to commonly prescribed drugs.

There are such major differences between drugs in their reaction-producing potential, as, for example, with blood dyscrasias. Considering the total number of patients exposed to the antihistaminic agents or the salicylates, the incidences of reaction are so low that the differences between them are insignificant when applied to any individual patient. The truth is that each has been followed by development of aplastic anemia and each must therefore be suspected.

Although it is true that statistically speaking a large, as compared to a small, series usually carries greater validity, the physician is concerned with the question of scientific reliability. A series is reliable on the basis of the pattern of the study and not on its size alone. In evaluating reliability, the physician must chiefly be concerned with the composition of the series, because there are so many patient factors which contribute to the development of the so-called toxic reaction.

Thus, in reviewing studies of the purported toxicity of the mercurials, Kaufman[39] notes that the "moribund condition of the patient and other factors leave room for doubt about the role of the mercurials," suggesting that moribund patients should be segregated in such studies.

Similarly, in discussing the studies of the supposed toxicity of the anti-arthritic agents, Bunim[14] states that patients with rheumatoid arthritis are "often subjected to prolonged medication . . . that may predispose them to serious complications. Possibly the hematopoietic and gastrointestinal organs of rheumatoid patients are especially vulnerable."

To re-state a point we have made elsewhere, an arthritic patient is more than a constellation of aching joints.

The basic question is emphasized in a recent editorial[21] in the *British Medical Journal* which inquires whether different observers are similarly defining "toxicity." Commenting on the apparent differences in results with identical drugs, the editorial says: "It seems probable that the variation of incidence of toxic symptoms is a reflection of the difference in the observers, or in the conditions of observations. If so, too much attention should not be paid to the percentage of toxic reactions as an indication of risks of using the drug."

It would certainly contribute to better communication if, instead of lumping together reactions of all types, and citing a general toxicity rate, reactions were classified into such major groups as: (1) Very serious and potentially fatal; (2) major toxicity, requiring cessation of treatment; and

(3) minor reactions with elective continued treatment. In this last category, perhaps a further distinction might be made between minor reactions of no great significance and those which are the first step of a sensitization process or otherwise portents of more serious consequences following readministration of the drug.

In addition, no matter how large the series of patients observed, we cannot escape the fact that, in toxicity as well as in therapy, we are always faced with the problem of the placebo reactor. As Beecher[6] showed, the administration of a placebo was followed with 25 per cent of the subjects reporting headaches; 10 per cent, nausea; 18 per cent, fatigue, and an amazing 50 per cent, drowsiness. Wolf and Pinsky[73] note the occurrence of major reactions to placebos as weakness, palpitations and nausea in one patient; in another a diffuse rash—itchy, erythematous and maculopapular; and in a third, epigastric pain, diarrhea, urticaria and angioneurotic edema of the lips. It has been noted by Wolf[72] that placebo effects often include objective changes, "which may exceed those attributable to potent pharmacological action," a fact amply documented but too often ignored in generalized reports of the alleged toxicity of chemotherapeutic and especially antihistaminic agents.

This is especially droll when the reports are said to have been taken off by an IBM system. A rabbit cannot be pulled out of a hat unless the rabbit has first been placed into the hat. The use of the machine adds speed but not validity to the published results. The same strictures hold true for the statistical methods usually applied. When a reaction *is not* a reaction, it is meaningless to tell us what the chances were that it might or might not have happened by chance. And when a reaction *is* a reaction, we have no right to subject the same patient to a series of such reactions or a series of patients to such similar reactions in order that the reaction rate may become "significant," especially in those experiments in which the statistician was called in at the end of the study instead of at the beginning.

The significance of the "placebo factor" is illustrated by Freyberg's[28] comment: "It has been customary to consider all abnormalities occurring during gold therapy as manifestations of gold toxicity. This is not justified as shown by observations of Fraser[26] who found that nineteen (27 per cent) of forty-nine patients among the control group who received no gold had what was considered by the physician as 'manifestations of toxicity.'"

The aspect of the subject was considered of such importance that in October, 1955, the Academy of Psychosomatic Medicine held a three-day symposium devoted to the "Psychosomatic Aspects of Drug Administration." Plans are under way to publish the papers presented in book form.

CASE REPORTS

Careful studies on large series of patients are as rare as are good epidemiologic surveys. Unfortunately, almost all of our data concerning reactions to drugs comes from original reports of one or several cases, and the gathering together of such reports into review articles.

The case report has been the subject of considerable discussion. It has been criticized most recently by Denber[17] who warns of "therapeutic inertia" as an inevitable consequence of continued reports of fatal reactions, in one case following chlorpromazine administration. He points out that, "It can be predicted that severe reactions and fatalities will occur among hundreds of thousands of patients receiving any particular medication. It

is of the utmost importance to view these incidents in the context of the entire therapeutic situation." The individual case report has been defended on the grounds that[22] it serves to "draw attention to a problem that may only be in need of further study, or that, on the other hand, may truly prove to be a timely warning. . . ."

The reports of one or several cases of supposed toxic or allergic effects, following the administration of a drug, if properly studied so that the relationship of drug and reaction have been truly established, are of unquestioned value to the student of drug reactions. As a communication to the clinician, however, their value is not clear because, instead of being applicable case reports, almost without exception, they pose questions that they cannot, by their very nature, answer.

On this point, the *New England Journal of Medicine*[23] has commented editorially on the attention given to such reports in both the medical literature and at medical meetings: "Unless these reports are carefully considered in context, including such data as the number of patients to whom the drug has been given, the amount prescribed and the number of lives saved, incorrect impressions are imparted to physicians. . . . There is danger in viewing case reports with alarm unless they are sufficiently broad in scope to include the indications, limitations, and contraindications of the drug under criticism. The busy practitioner, with neither time nor facilities to evaluate the broader aspects of one of the newer agents, may be influenced to withhold the drug when it might be sound practice to administer it."

The individual case report of a blood dyscrasia will serve as an example. Since it would appear from reliable studies that almost any drug is capable of producing a blood dyscrasia, it would follow that every drug should be used as though it were so capable. As noted by Barr,[4] the function of the bone marrow can apparently seriously be disturbed in almost an identical manner by antibiotic agents, sulfonamides, antihistaminic agents, antimalarials, barbiturates and some of the heavy metals. In addition, Osgood[48] specifically lists anticonvulsants, antimicrobials, antithyroid agents, sedatives, spasmolytics and others.

What is true of the epidemiologic survey and of the studies of the series of patients is therefore also true of the individual case report. Because so many drugs are associated with blood dyscrasias, and because this must be known to all physicians independently as to whether they have happened to have read a particular case report, there would seem to be a question as to the value of such reports. If, again, every physician regarded every drug, however innocent its reputation, as a possible cause of blood dyscrasias, the individual case report, instead of being a cause for alarm, would then serve a valid purpose as a starting point for epidemiologic studies (or for the type of study which would prove the relationship false). The question is raised because we may not be alerting the clinician, but rather we may be disarming him. It is as though we were to warn a child that "this gun is loaded." This statement may disarm him regarding any other gun we have not specifically mentioned. This is, in fact, how many shooting accidents occur. We must be trained to handle *all* guns as though they were loaded.

Similarly, if physicians were to regard all drugs as though they could cause either blood dyscrasias or anaphylaxis, we would certainly see fewer drug reactions and those less serious.

It is the point of view that some drugs are toxic and others nontoxic

which is dangerously disarming. Unfortunately, the single case report, or the collection of such reports into review articles, concentrating as they do on one drug, unintentionally tend to communicate the implication that the alternative drugs, by the mere fact that they are not discussed with equal emphasis are, in some way, free of risk.

What we really need to know is the frequency with which we may expect a particular type of reaction from a particular type of drug. This cannot be discovered from the most carefully worked up case report, or the grouping of such reports into reviews. We need broader surveys, giving us (1) information on the number of people who have taken the drug, and (2) the number of patients in whom a particular type of reaction has been (by reasonable standards of precision) noted.

REVIEWS

The impression derived from the original case reports may be compounded by the review article which culls from the literature the reports of reactions following administration of the drug. Again, serious reactions reportedly following commonly prescribed drugs are sufficiently frequent so that such review articles can be written concerning virtually any widely prescribed medicinal agent. It is with this point that one would hope the clinician would be familiar. In the world literature can be found reports of deaths attributed to any drug, alphabetically beginning with acetylsalicylic acid and ending with zinc oxide.

The fact that from time to time a review article will attribute a series of deaths to a drug does not truly add to the clinician's knowledge. Nor should it cause him to prescribe an alternate drug. In time, he may see a review of a series of deaths from the drug of second choice. The reactions are there. They await only the reviewer to collate the frequently unproven case reports. The report does not change the properties of the drug. If the physician's decision to administer a drug was correct before reading the report of a few serious reactions, it was just as correct afterwards. By the same token, the fact that no one has recently chosen to review the world literature on any particular drug does not make its prescription any safer for physician or patient.

All of the foregoing assumes, of course, that either the case report or the review article is qualitatively as good as it can be. This complex subject will grow in importance as more potent drugs become available.

Many excellent clinicians, blithely ignorant of reports published, for example, in a foreign literature, have safely and effectively prescribed the very drugs the reports labeled as dangerous. This may be explained by the fact that they have familiarized themselves with the proper method of patient selection and correct dosage levels, and coupled this with good clinical sense in the recognition of early reversible symptoms of reaction.

We can say without qualifications that there are few instances in which, on the basis of a single case, or a group of cases, a particular drug can validly be held causatively responsible for a serious reaction. If all the cases in which the patients were not properly selected for treatment with this drug, or the dosage was not carefully chosen with consideration for reaction potential, or the subsequent course of treatment was not adequately managed, or careful observations of the first sign of reaction were not made—if these were eliminated from the reports of toxicity—there would indeed be few cases of which it could be said that the drug actually *caused* the reaction.

As a matter of future reporting, the concepts of contraindication may require broadening. We must know enough about the newer chemotherapeutic agents not to administer them as they have so often been administered in the reported cases of presumed toxicity. Modern treatment is not merely a question of giving a particular drug to a particular patient. It has become a problem of how to give the drug to the patient for whom it is indicated and exactly as needed. Those reports of cases of misadventure, in which the drug has not been properly administered, and which do not point up the abuses involved, do not help to inform the physician as to how the drug is to be given, and may actually discourage its prescription for patients for whom it may promote recovery or save life itself.

In this sense, good case reporting can be of considerable value, if only by helping to evolve a clearer concept of the conditions under which a drug may be administered with minimal risk, or by establishing the specific conditions which increase that risk. It is to this problem of more adequate reporting that we will return.

WHAT WE KNOW

It might be interesting at this point to raise the question as to what we truly know of the toxic reactions to commonly prescribed therapeutic agents. More properly the question might be phrased: What accurate information is available to the conscientious clinician so that he may exercise the type of judgment expected of him whenever he prescribes a chemotherapeutic agent? It is neither feasible nor necessary to answer this question for every type of drug. The sulfonamides, penicillin, the antiarthritic agents and chlorpromazine will serve to illustrate revelant points concerning present-day supposed facts on drug toxicity. It becomes obvious that the information obtainable conforms to a general—and not too satisfactory—pattern.

THE SULFONAMIDES

The earliest of the new anti-infectious agents, the sulfonamides, have certainly been the most thoroughly studied. With the thousands of reports available, what do we really know of the toxicity of the different drugs in this group?

Although there are no exact figures as to the number of patients who have received these drugs during any given period, Hawking and Lawrence[34] estimate that as far back as 1941 probably 10,000,000 to 15,000,000 patients were treated with sulfonamides, and that by 1943 enough of these drugs had been produced in the United States alone to treat 130,000,000 patients.

During 1941, in New York City, there were twenty-eight reported deaths reputedly due to sulfonamides. This led Sutliff et al[61] to observe that "many deaths from sulfonamide toxicity were not being reported." How familiar does this phrase sound today! And this statement continues to be cited, although there is the comparative observation of Yow[75] that, at the Jefferson Davis Hospital of Houston, "during the last five years, 500,000 grams of sulfonamides have been used yearly with no examples of renal toxicity" and, "no instances of agranulocytosis or of aplastic anemia" traceable to sulfonamide therapy.

In confusing contrast is the review by Denny and Martin,[18] who state that in five of six cases of aplastic anemia, admitted to the Children's

Hospital in Pittsburgh during a thirty-month period beginning in 1942, sulfonamide drugs had been prescribed. Only one such patient had been admitted to the hospital during the previous fourteen years. And yet, from the Welch *(op. cit.)* study on blood dyscrasias we learn that in those cases reported in the FDA survey covering 1949 to late 1953, the sulfonamides had been prescribed in 130 of the 1,448 cases reviewed, and that in thirty-eight patients a sulfonamide alone was the only drug involved. Of the 212 patients suffering from aplastic anemia, following drug administration, sulfonamides had been prescribed in forty. In eleven cases a sulfonamide was the only drug taken.

In the 103 deaths from agranulocytosis reported following drug administration in Denmark from 1952 to 1954, "sulfonamide preparations" were responsible for thirteen, a number exceeded only by Pyramidon.® It is significant that following the extensive research *(op. cit.)* that resulted in their excellent monograph concerning the sulfonamides, Hawking and Lawrence concluded, "The incidence of fatal toxic complications in man is difficult to determine. . . ." They point out that the incidence of fatal toxic complications is "undoubtedly very small." The question of what is meant by "very small" is somewhat complicated by a recent observation in "A Re-evaluation of Sulfonamide Therapy" by Yow,[75] in which the author concludes that the toxicity to the newer sulfonamides is, "no greater than that seen with antibiotic therapy." This type of conclusion is surely neither specific knowledge nor information upon which decisions can be based involving the concepts of either optimal therapy or calculated risk, since no one knows what the toxicity values of antibiotic therapy may be.

One of the chief sources of the difficulty is the lumping together of the sulfonamide drugs, so that we do not know with which of each any specific number of patients has been treated. Since it has been the contention of students of these drugs that (as Yow points out), "most of the serious complications, such as hematological disorders, have been reduced to less than 0.1 per cent by the use of sulfadiazine, it is difficult to assess the significance of any figures attributed generally to 'sulfonamides.'"

What is so often forgotten is that the characteristic action of a drug is closely related to its chemical structure. Sometimes this relationship is a broad one so that with some molecules many variations can be made in the basic structure without losing characteristic activity, as with the cocaine derivatives. But with others, this relationship is so narrow that the slightest alteration in structure will cause the molecule to lose its pharmacologic activity. In some, optical isomerism alone changes pharmacologic action, as for instance with the ergot alkaloids. Some compounds possess multiple actions, and changes in configuration alter some and not others, since, apparently, different parts of the molecule are concerned with specific activity.[31]

The importance of the difference in chemical structure of drugs of the same group is documented by the fact that the degree in which sulfanilamide, sulfapyridine, sulfadiazine and sulfathiazole are bound to plasma protein ranges (at therapeutic concentrations) from 18 per cent for sulfanilamide to 75 per cent for sulfathiazole.

In the plasma, the clinically used sulfonamides, including sulfamerazine, exist in several forms: acetylated, which is inactivated, and the free, which is either bound or unbound. The bound drug is temporarily out of

combat but remains a reservoir of available drug. The level of activity is proportional to the concentration of unbound drug. This, in turn, exists in equilibrium between the ionized and the un-ionized molecules, but the interpretation of the effect of this equilibrium on activity is difficult to assess in the light of studies disproving the early concept that the antibacterial activity is simply proportional to the concentration of ionized drug. The newer arylated or highly soluble sulfonamides again possess different characteristics. However, Geiger[29] seems to take exception to the idea that one of the newer sulfonamides, Gantrisin,® is significantly less prone to cause blood dyscrasias. He cites ten cases of blood disorders (leukopenia, thrombocytopenic purpura, and petechial hemorrhage) associated with its use, as reported in the literature between its introduction in 1946 and his report in 1952. These again may not be related to the use of the drug, and their validity can be questioned as much as those disorders ascribed to Chloromycetin and Butazolidin.

Continuously reported are other serious types of toxicity following sulfonamide administration, namely—renal tubular irritation and blockage. The earlier communications of these effects of sulfonamides presumably do not apply to the newer highly soluble sulfonamide compounds following administration of which crystalluria has been rare. There is also the question of the use of mixtures of these drugs, following Lehr's[42] confirmation of the concept that the saturations of the several sulfonamides are independent of each other and not cumulative.

In sensitization responses, intensively studied by Lehr,[42] the dosage was a significant factor and directly related to the number of reactions observed. In an analysis of symptoms occurring during the sulfadiazine treatment of 1,357 patients at New York Hospital, such relationship between dosage and incidence of toxic effects was demonstrated by Plummer and Wheeler[51] with the latter more closely related to higher blood levels. The percentage of reactions ranged from 1.8, with blood concentrations of less than 5 mg/1000 cc, to 14.8 at levels of more than 15 mg/1000 cc.

Hawking and Lawrence (*op. cit.*) state that dosage or blood concentration is not important in the causation of acute hemolytic anemia. With clinical agranulocytosis, dosage does apparently play an important part. A survey of sixty cases, forty of them fatal, recorded in the world literature by 1941, reveals that almost all followed 50 grams or more administered over a period of eight to twenty-one days. And yet, it has been argued that agranulocytosis is due to allergy and sensitization!

Are sulfonamides toxic or are they safe, and if toxic and allergenic, for whom, when, and after how much?

The available data on the sulfonamide drugs suggest the importance of knowledge of specificity within the drug groups and of dosages as prerequisites for advancing our understanding of toxicity. Many other conditions associated with or causing toxicity are unresolved by available data.

This is also true of the various dosage forms of penicillin, the several broad spectrum antibiotic agents and other drugs which, no matter how closely they may be superficially related, or apparently unrelated, seem to have quite specific properties, both as to effectiveness and to toxicity.

PENICILLIN

In 1953 the FDA survey[70] covering ninety-five hospitals in eleven cities, uncovered eighty-four anaphylactoid reactions, twenty-four of them fatal,

following penicillin administration. It has otherwise been estimated that there were 100 to 200 anaphylactoid reactions yearly from penicillin, of which approximately 30 per cent were fatal. Another review of the literature[64] uncovered more than 130 reports of severe anaphylactic reactions, including forty fatalities.

Significantly, not one of the anaphylactoid reactions uncovered in the FDA survey had ever been reported in the literature. This suggests that the case report approach, as compared with the large scale survey, is not a good guide in the evaluation of drug toxicity.

The impact of these reports has led to comments such as Alexander's[1]: "Little has been gained in terms of hypersensitivity by the replacement of the arsphenamines by penicillin in the treatment of syphilis." This observation, however must be compared with that of Smith et al,[59] that "although one of 93,000 patients treated for venereal disease with penicillin died, the combined arsenical and penicillin schedules were followed by one death in 8,700 patients." There is no question that the literature on penicillin reactions has, to some extent, diminished the use of the drug, and it has been observed as previously noted, that "recent pleas in the medical literature, condemning the indiscriminate use of intramuscular penicillin, have on occasion induced physicians to withhold indicated treatment for syphilis." (Smith et al, *op. cit.*)

If the literature can be trusted, penicillin sensitivity is increasing at the rate of approximately 1 to 2 per cent a year, so that the overall problem will, if anything, grow more serious.[11] There are considerations which suggest that the problem is also becoming more complex.

For one thing, a closer examination of the literature concerned with penicillin indicates that, as in much of our reporting of toxicity, there has been an unfortunate tendency to group patients together as though they were physiologically co-equal, which they certainly are not. We have, for example, pointed out elsewhere[12] that, while the reaction rate to injected penicillin in nonallergic patients is 5 per cent, it is approximately three times greater in allergic subjects.

Independent studies have shown the grave necessity for classifying patients as allergic or nonallergic. Berkowitz et al,[7] studying the twenty most widely prescribed drugs in a pediatrics practice, were able to demonstrate that the incidence of allergic reactions for the allergic group was 20.0 per cent as compared to 2.4 per cent for the nonallergic group, and that interestingly enough the incidence of "side reactions" was 36.0 per cent in allergic chidren as compared to 3.5 per cent in nonallergic children. For example, following penicillin, the rates of allergic reactions were 10.0 per cent in allergic children and none in the nonallergic. Greater differences existed between the two groups on a percentile basis in regard to "side reactions." The application of this knowledge to the reporting of toxicity of drugs would both significantly modify our approach to drug administration, and as well the reporting of the incidence of all types of drug reactions.

Smith et al (*op. cit.*), have also observed a significant age factor, with patients in the ten to nineteen age group tolerating penicillin better than those in older groups up to fifty, at which age the reaction rate may again tend to decrease. Interestingly, these observers also note a true sex differential, with a greater incidence of reactions in females than in males, and a "race" differential with a greater incidence in "Caucasians" than in "Negroes."

In 1948 we[11] pointed out that new types of penicillin appeared to have different reaction rates than the older dosage forms, a fact which, as in the case of the sulfonamides, has been obscured by references in the literature to "reactions to penicillin." Thus, a recent study[59] suggests that, while the reaction rate to procaine penicillin in a series of 12,179 patients was 0.80 per cent, the reactions to benzathine penicillin G were 0.24 per cent.

Significantly, in the FDA study[68] there were fifty-five anaphylactic reactions due to procaine penicillin of which eighteen were fatal, while from penethemate injections, used very infrequently as compared to procaine, there were twenty-six reactions, five of them fatal.

The available data on penicillin suggest that, if reporting of toxicity is to serve as a guide to clinical judgment, it is important to do more than collect generic observations on penicillin. It is necessary to know *when* the reactions occurred. Valid and useful data will also be derived from studies which differentiate between the specific drugs and dosage forms, and note the characteristics of the patients, and the reaction rates of different groups of individuals in the patient population.

The question of dose is important because of the obviously allergic nature of the fatal reactions to penicillin. Characteristically, allergic reactions are seen in response to infinitesimal quantities of the antigenic substance involved. This problem of the presence in the Salk vaccine of minute quantities of penicillin has been raised. Siegal[58] concludes that the penicillin content is "negligible." However, Bierlein[8] has observed a patient who went into anaphylactic shock when tested intradermally with 0.000003 of a unit of penicillin. Passive transfer tests were positive with 0.003 units.

THE ANTI-ARTHRITIC AGENTS

In the management of arthritis, the reported incidence of drug reactions has dominated the choice of agents used and apparently will continue to do so in the foreseeable future.

The situation is complicated by the fact that the disorders involved are chronic but not fatal, and the drugs prescribed provide symptomatic but important relief. In this context, the most meticulous evaluation of toxicity is needed to guide the clinician. On the basis of present reporting, what valid conclusions may be drawn?

To begin with, the salicylates serve as a basis for "conservative therapy" and certainly patients who can be maintained on acetylsalicylic acid will not be exposed to other more potent drugs. It is interesting to note that acetylsalicylic acid has been so widely used (more than 9,000,000 pounds yearly in the United States), and for so long a time, that the reporting of such reactions as do occur is not an indication of its toxicity. The author has, for instance, never reported on acetylsalicylic acid sensitivity although his present practice embodies more than 100 patients who cannot tolerate the drug in the most minute quantities.

It is interesting that, although prescribed for many years, it was not until 1951 that the paper by Feinberg and Malkiel[24] established that acetylsalicylic acid could become attached to protein and thus become antigenic. Butler, Harrington and Yuill (in 1940) by the use of aspirin-conjugated-protein had, in rabbits, obtained precipitins to aspirin.[18]

All allergists are familiar with the violent paroxysms of bronchospasm which can occur in asthmatic patients following the ingestion of small quantities of the drug. These, occasionally, as we need no reminding,

terminate in anaphylactic shock, as noted by many observers including Cooke,[16] Dysart,[19] and Francis et al.[25]

Recently, reported in the French literature by Blamoutier[9] are eleven cases, two fatal, of allergic manifestations after ingestion of acetylsalicylic acid in hypersensitive patients. Almost all presented a history of allergy, and some patients were asthmatic. Since this type of hypersensitivity has frequently been demonstrated and the mechanism for it partially explained, it is difficult to accept the few reported fatal reactions to acetylsalicylic acid as in any way truly representative of the actual number in a population in which relatively few have not been exposed to this potentially allergenic drug.

Of more concern, because of the large doses used in arthritis, is the relationship between salicylate therapy and hemorrhage, especially gastric bleeding. In a recent study[46] of 166 patients with hematemesis, acetylsalicylic acid seemed, at least in forty-three, to be a precipitating factor. Here, once more, we possess no epidemiologic evidence of the exact incidence of this type of reaction.

Turning to the more potent drugs in this field, although the hormones, the gold salts, and phenylbutazone have been prescribed for millions of patients, we do not, here also, for the most part have any epidemiologic studies defining with statistical validity the incidence of toxicity. Nor do we have any significant data dividing the population into significant groupings from which we can predict with any accuracy who will do better on one drug and who should be given another.

The information available consists of very few studies on series comprising several hundred patients, added to an assortment of individual case reports, together with occasional reviews of these cases. The conclusion, after reviewing the literature, is that the evaluation of the toxic potential varies greatly with the point of view of the author.

The reports on the toxicity of gold salts, for example, are a case in point. The over-all toxicity incidence in various series reported ranges from 4.6 to 100 per cent. Robinson et al[55] point out, "This wide variation probably depends on several factors, including the preparation used, the dosage employed, the caution exerted during therapy, and consideration of what reactions are worthy of note." What this review concludes of gold salts can well be said of the other drugs similarly used in arthritis.

First, as to the compound and the dosage employed: with each of these drugs, the early dose levels prescribed were higher than those which are currently recommended. It would seem elementary, therefore, in the evaluation of the toxicity of these drugs to segregate the patients' reactions in accordance with the dosage levels at which they occurred. The doses administered are not always mentioned in the original report.

As for "the caution exerted during therapy," this includes not only proper dosage levels but rigorous selection and management of patients, and above all, the closest attention to the first signs of toxicity. The responsibilities would seem to be obvious, although not always accepted. Ragan[52] has emphasized the need for the physician to "take the time to know his patient, work with him toward the solution of his problems, utilizing both common sense and empirically gained knowledge." Contrast this with a report of a case which terminated fatally.[27] It is stated, "It is obvious that treatment with phenylbutazone should have been permanently discontinued at this point, but six weeks later it was resumed at the patient's own request." It would seem clear that Fraser,[27] who disregarded unmistakable warnings of toxicity when they were minor, and instead

persisted with the drug because the patient requested it, would encounter and report a greater rate of toxicity than one who followed the therapeutic approach outlined by Ragan.

Batterman[5] has recently commented on the reluctance of physicians to continue to prescribe drugs when their only experiences occurred during the early years of their investigation, "when insufficient knowledge was available to guide the physician in prophylactic measures or recognition of the early signs of toxicity."

There is then the question of "what reactions are worthy of note." There is an increasing awareness of the fact that the disparity of observations on toxicity has something to do with the disparity in points of view of observers. [Fraser[26,27] and Freyberg (in Comroe's Arthritis[28]), among others, have commented on this point, as has editorially the *British Medical Journal*[21] and, as well, Denber[17] in a communication to the *Journal of the American Medical Association*]

In the first instance, does the observer include in his calculations those reactions in which there is no clear-cut evidence that the drug was responsible? Mauer[44] in a recent review of supposed fatal reactions following phenylbutazone, includes some cases in which the original authors themselves hesitated to attribute the reaction to the drug. Are early cases of reactions now regarded as due to overdosage to be added together with the reactions following modified dosages? What then of the reported reactions attributable to placebos? Are they also to be subtracted?

Most important of all, however, is the question of segregating the minor reactions from the major. If one accepts the present and past reports at face value, toxic reactions of all types occur following gold salts in 45 to 50 per cent of the patients; following phenylbutazone in 35 to 40 per cent; while with cortisone they range from 46 to 72 per cent. Since these percentages include all reactions, varying from minor gastrointestinal discomfort to fatal blood dyscrasias, the question remains as to what guidance they give the clinician. If they serve to promote greater caution and conservatism in the use of these drugs, they are of some value. But, if they serve to encourage the use of conservative therapy, such as salicylates, in cases in which the patient is left in considerable pain and functionally crippled, then we are involved with the philosophical problem of the responsibility of the physician. As Ragan (*op. cit.*), from his conservative point of view, says, "Pain brings the patient to the physician, and its control must be attempted." In the control of pain which, in so many of these cases is severe and of long duration, totaling percentages of minor toxic reactions, is hardly a mature approach."

If one, therefore, analyzes the available data, and separates out the major reactions (those requiring withdrawal of the drug), the reports are more useful. Bunim (*op. cit.*), in a survey of the recent literature, points out that gold therapy was discontinued because of toxicity in an average of 9 per cent of a recent series (with a range of 3 to 24 per cent), and phenylbutazone was discontinued in 12.1 per cent. He cites the analysis of Hench and Ward[35] who show that in seven reported series, cortisone was discontinued in 10 per cent of patients because of undesirable side effects or of complications. In the ARA comparative study of cortisone,[38] the drug was withdrawn in 23 per cent of cases because of an untoward effect.

In choosing from among these drugs, the physician should obviously be most deeply impressed by the reports of fatal reactions which have occurred with each of the three. Broad statistical studies in which such re-

actions are related to the total number of patients exposed to these agents, are not available, except for phenylbutazone. In the case of gold salts, fatal reactions have been reported by Robinson et al (*op. cit.*), in as high as 3 per cent during the early use of this drug, but are reported to have decreased to approximately 0.4 per cent. Ragan and Tyson[54] report two deaths in a series of 460, and Ragan and Boots[53] report two deaths in 600. The highest fatality rate is that reported by Hartfall et al, seven deaths in 900 patients treated (cited in Steinberg, C. L.: "Arthritis and Rheumatism," p. 132, New York, Springer, 1954) while in fourteen series reviewed by Bunim (*op. cit.*), including 4,086 cases analyzed by Freyberg (*op. cit.*), there have been no deaths since 1936.

In the case of phenylbutazone, whose toxicity has been the subject of comment since its first introduction, Mauer's survey of the world literature reports nine cases which had occurred in the United States and adds a case of his own and one additional fatality in a personal communication. In this instance, we do have an estimate of the total number of patients exposed to the drug in this country, more than 3,000,000. Thus, if one were to accept as valid all the cases cited, the rate of fatal reactions on a comparative basis is much less than that of gold or hormonal therapy. Commenting on the problem of fatal reactions encountered with this drug as reported in the literature, Wornom and Swineford[74] have recently said that, based on their experience in their own clinic, "figures compare favorably with the two deaths and twenty violent, alarming, anaphylactic reactions from aspirin, and the eleven deaths from cardiovascular accidents in 165 cases while taking cortisone."

With cortisone, we unfortunately do not have over-all statistics on the number of patients exposed. In the ARA co-operative study of cortisone (*op. cit.*), in twenty-five clinics in the United States and Canada, in twenty-three of 446 patients (4 per cent), death was "possibly related to cortisone therapy." Weinberger[67] reports that in a one year period at the Veterans Administration Hospital in Los Angeles, "where every effort to safeguard the administration of this drug was made, there was an 8 per cent mortality."

CHLORPROMAZINE

Chlorpromazine is an interesting case in point because the attitude toward it is in the process of formation, and the present evidence suggests that unless there is some unpredictable change, it will fare no better than other major drugs. It has been termed by Tuteur[62] "a miracle drug." Ayd[2] says categorically, "no physical harm results from prolonged moderate use." Nevertheless, case reports of serious toxicity continue to appear and seem steadily to increase in number.

Such is the apparent contradiction involved that, in the literature, there are some rather sharp comments on the literature itself. Thus, Ayd observes (*op. cit.*): "An assessment of these reports is difficult because some are over-enthusiastic, premature, uncritical and unscientific, made after a brief clinical trial while others are hypercritical reviews based on insufficient evidence." Denber (*op. cit.*) emphasizes this confusion by commenting on "the familiar pattern of enthusiastic reports, lethal side reactions and therapeutic paralysis," in connection with this drug, and predicts that "continued reports of lethal reactions in 'one case' will activate unconscious anxieties and fears," and so, he suggests, invalidly curb the use of the drug. He warns particularly that "the danger of 'one case reports' with sweeping conclusions is evident."

Chlorpromazine, as toxicity reports note,[15] is related chemically to phenothiazine, a drug which has been reported to produce liver disease (toxic hepatitis) and acute hemolytic anemia, reactions which have "precluded its wide application in medicine."[32] Here, then, is the familiar pattern of "guilt by association" which, whatever is validity, does tend to belie the fact that chemotherapeutic progress has, to a large measure, depended on the skill with which chemists have been able to synthesize variations on toxic molecules to produce others less toxic. It may be that these attempts are only relatively successful, but it is also true that molecular modification has produced some rather significant changes in toxicity which must be evaluated in their own right. The issue is only confused by damning a drug because of its chemical resemblance to a more toxic relative, especially since some of the cases of "toxic hepatitis" may be coincidental cases of infectious hepatitis.

In the case of chlorpromazine apparently more than 4,000,000 patients in the United States alone have received the drug, and the world figure is greater than 5,000,000. The U. S. Tariff Commission statistics[63] indicate that enough of the basic raw material for chlorpromazine was brought into the United States in 1954 to produce over 100,000,000 tablets in the dosage most frequently used.

At this time (February 1, 1955) we have found forty-six reported cases of agranulocytosis supposedly associated with chlorpromazine administration, and there are undoubtedly others which our search did not reveal, and others again not recognized and, if recognized, not reported. The point is that when this incidence is related to the 4,000,000 patients who have received the drug, it is hard to consider these, if true, other than clear cases of idiosyncrasy. Since the occurrence of this type of idiosyncrasy is unpredictable, in any one patient, it is difficult to see how "the greatest good for the greatest number" can be accomplished by discouraging the use of chlorpromazine, a result which continued reporting of this type will certainly effect.

It would be interesting to poll patients or their families to learn whether the psychotic symptoms for which the drug is effective are not more undesirable to them than the 1:100,000 chance of a possible blood dyscrasia, although the dyscrasia might inevitably be fatal which it is not.

A paralysis agitans-like syndrome has also been reported by Goldman[30] in as many as fifty-four cases out of a series of 500. The symptoms vary from some rigidity and stooping to characteristic tremors, gait and speech difficulties, but apparently subside when the drug is withdrawn.

Apparently, reactions can be modified by adjusting the dosage. Disturbing as such reactions may be, again they raise the basic question as to whether the risk of such transitory side effects is a more serious consideration than the psychotic manifestations for which the drug was used. At least one observer has given this matter serious consideration and has concluded that many patients at least "prefer to suffer (side reactions) for a relatively brief period to achieve freedom from psychotic manifestations."

This is the new problem which the clinician increasingly finds himself facing, and under these circumstances, withholding the drug is too easy a solution. Is the physician not in a position very similar to that of a surgeon facing an elective operation?

Finally, there is the involved question of jaundice which in some series (Azima et al,[3]) has reached a total of 5 per cent. Yet, another observer Goldman (*op. cit.*) reports one case in 500 patients. In some cases the jaundice is of brief duration, but cases have been described (Kohl et al[41]

and Von Onman et al[65]) in which the symptoms have persisted for months. Moyer[45] notes that clinical recovery occurred in all twenty patients reported by Kelsey et al, although abnormal hepatic function, as determined by laboratory studies, persisted in many others. He mentions one patient who died while taking in excess of 1,000 mg daily.

There is one case report (Broadman[10]) of fatal toxic hepatitis in which chlorpromazine was implicated, but there was also valvular heart disease with congestive failure, and it is possible that passive congestion of the liver may have increased hepatic susceptibility to the toxic action of chlorpromazine.

One of the most recent papers on chlorpromazine (Ayd, *op cit.*) notes "the fear of possible development of hepatic damage with chlorpromazine has not materialized" and urges, "These reactions should not panic the therapist into prematurely terminating treatment."

In the case of chlorpromazine, the confusion in toxicity reporting has come home to roost. We now have observers as Hodges and Lazerte[36] reporting that serious reactions (jaundice) are "a more frequent complication of chlorpromazine therapy than the published reports indicate" while another comments sharply on the "unwarranted criticism of these drugs," and incidentally blames much of this criticism on the medical profession, since this and related drugs "are being used on patients totally unsuited for them by physicians who supplant clinical judgment for expediency" (Ayd *op. cit.*).

Finally, Denber's[17] "Letter to the Editor" predicts "reports of a rather alarming nature . . . may well open a pathway for a counterattack by therapeutic nihilists."

These wide disparities of opinion, casting doubt as they do on the judgment of the medical profession and its research workers, may be a tribute to free medical journalism. They are hardly a tribute to good medicine.

END OF PART I

(The second part of this paper on "The Reporting of Toxicity" will concern itself with how toxicity should be reported.)

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PROPERDIN

(Continued from Page 205)

For the time being, all this is of no immediate practical impact. But the potentialities of these investigations have certainly roused the interest of the immunologists, as witnessed at the recent Conference on Natural Resistance of the New York Academy of Sciences, where the presently available data were presented by Pillemer and the growing group of laboratories cooperating with him. Information pertaining to resistance to infection and shock merits also the attention of physicians concerned with immunologic disease.—*A.J.W.*

FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Cologne, Germany, will be the site of the Fourth International Congress on Diseases of the Chest of The American College of Chest Physicians, August 19-23, 1956. The meeting will be held under the patronage of the Federal Chancellor, Dr. Konrad Adenauer. Eighty-six countries will be represented. Officers of the congress will be: Prof. Dr. med. Dr. h.c. Gerhard Domagk, president; Prof. Dr. med. Dr. h.c. H. W. Knipping, vice president; Prof. Dr. med. J. Jacobi, general secretary; and Prof. Dr. med. J. Hein, chairman of the executive committee. The subjects to be discussed deal with the problems of coronary diseases, industrial diseases of the chest, tuberculosis, lung and heart function, and tumors of the mediastinum. Several outstanding foreign scientists and clinicians will present papers on these subjects. Official languages for the congress are English, French, Spanish and German. Further information may be obtained from the secretariat of the congress, Köln-Deutz, Germany, Messeplatz.

News Items

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians will hold its twenty-second annual meeting at the Hotel Sherman, Chicago, Illinois, June 6-10, 1956. The scientific program will include prominent speakers on all aspects of heart and lung diseases, symposia, round table luncheon discussions, seminars, and motion pictures. The popular "Fireside Conferences" held in 1955 will be repeated. At this session, more than fifty experts will be present to lead the discussions on many subjects of current interest in the specialty of diseases of the chest. Examinations for Fellowship in the College will be held on Thursday, June 7. All interested physicians are invited to attend this meeting, for which there is no registration fee. Copies of the program may be obtained by writing to the Executive Offices, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

FLORIDA ALLERGY SOCIETY

The Florida Allergy Society will hold its eighth annual meeting on Sunday, May 13, at Hotel Fontainbleau, Miami Beach, Florida. Dr. Harold Tuft of Denver, Colorado, will present a paper on "Rehabilitation of the Intractable Asthmatic Child"; Dr. Virgil Moon of the University of Miami will discuss "Dynamics of the Anaphylactic Reaction"; and there will be a panel discussion on "Clinical Investigation of Allergens Peculiar to the Tropics and Subtropics" presided over by Dr. Maurice Zivitz, in which Drs. Morton Hammond, George Gittelson, and Jack Rudolph, and Miss Lillian Fly will participate.

POSTGRADUATE COURSE IN INTERNAL MEDICINE

"Topics in Clinical Medicine" will be the subject of a six-day postgraduate course designed especially for physicians primarily interested in internal medicine, sponsored by the Department of Medicine of The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine, Baltimore, Maryland, May 7-12, 1956. Dr. A. M. Harvey, professor and director of the Department of Medicine, is directing the course which will be held in Hurd Memorial Hall, the hospital amphitheatre. Registration is limited to 150 physicians, and an all-inclusive fee of $100 will be charged. For information, write: Dr. Philip A. Tumulty, Department of Medicine, The Johns Hopkins Hospital, Baltimore 5, Maryland.

PHILADELPHIA ALLERGY SOCIETY

The following persons have been elected to direct the activities of the Philadelphia Allergy Society for 1956:

President.....Philip M. Gottlieb, M.D.
Vice President.....Edmund E. Ehrlich, M.D.
Secretary-Treasurer.....Eugene A. Hildreth, M.D.

SECTION ON ALLERGY—KINGS COUNTY MEDICAL SOCIETY

On May 1, 1956, the Section on Allergy of the Medical Society of the County of Kings will hold a scientific session at which the subject of "Modern Concepts of Allergy in Children" will be presented by M. Murray Peshkin, M.D., and discussed by Bela Shick, M.D. Officers of the Section on Allergy are: President, William Messer, M.D.; vice president, A. Irwin Kleinman; secretary, Harry Leibowitz, M.D.; and treasurer, Solomon Slepian, M.D.

THE NEW JERSEY ALLERGY SOCIETY

Officers of the New Jersey Allergy Society for 1956 are as follows: President, Lewis W. Brown, M.D., Newark; treasurer, Harry Hershey, M.D., Jersey City; and secretary, Frank H. Feldman, M.D., Newark.

RESIDENCIES IN ALLERGY AVAILABLE

The Kaiser Foundation Hospital, San Francisco, California, has available two approved residencies in allergy which offer an unusual opportunity for clinical training in allergy. The outpatient department in allergy has more than 60,000 patient visits per year, and there is a complete allergy laboratory to service this department, offering the resident an opportunity to learn the basic procedures in the preparation of antigens. The Kaiser Foundation Hospital has 225 beds and offers an exceptional opportunity for inpatient problems in the clinic of allergy. The salary for these residencies is $225.00 per month, plus $70.00 maintenance allowance. Applications should be made to Ben F. Feingold, M.D., Chief, Department of Allergy, Kaiser Foundation Hospital, 2425 Geary Boulevard, San Francisco 15, California.

BOUND VOLUMES AVAILABLE

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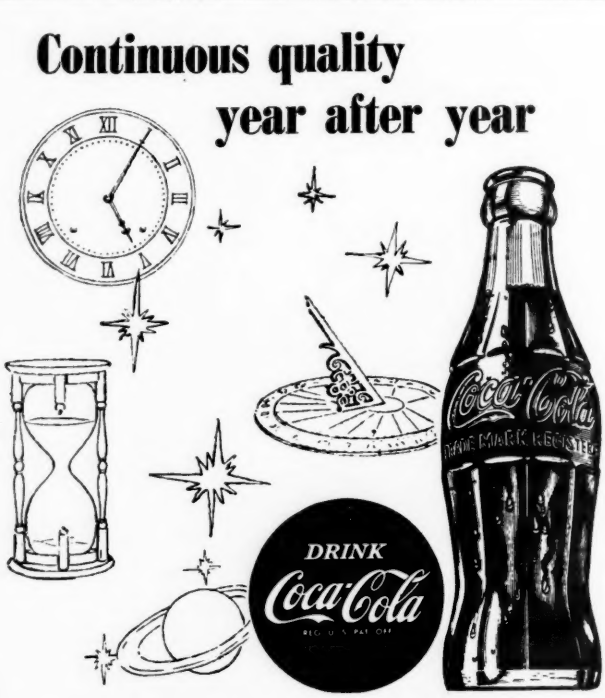

BOOK REVIEWS

YOUR HEADACHE and What to Do About It. Henry D. Ogden, M.D., Clinical Assistant Professor, Department of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana. Forewords by Horace S. Baldwin, M.D., president, American Foundation for Allergic Diseases, and Ethan Allan Brown, M.D., editor, ANNALS OF ALLERGY, 72 pages, illus., paper cover. New Orleans, Louisiana: Headache Study Group, P. O. Box 343, 1955. Price $1.00.

This book is intended to give aid in relieving headaches of all kinds, and describes the important types, causes, and treatment. With these clearly explained, it is possible for the headache victim to appreciate the causes and the necessary treatment. Modern medical management is based on consideration of the patient as a whole and his environment, to which both mind and body react. Throughout the book, scientific terms have been avoided as much as possible, but when their use is necessary, definitions are given to clarify the ideas which are presented.

The author made a cross-section survey of approximately 5,000 individuals, and this booklet is based on his experiences with these patients. Chapter 1 gives specific examples of why all headaches are not alike. All the chapters are short but very concise, and include research on the types of vascular headaches, the nose as a cause of headaches, frontal headaches, the influence of age, sex, and marital status. It is interesting to note that 78.7 per cent of the people in the survey, age twenty or under, had headaches, and that headaches declined in each decade so that those over age sixty had the least headaches. Seventy-one per cent of women, compared to 50.7 of men, suffered from headaches, and single people have more headaches than married people. The chapter on the influence of education and occupation shows that about 77 per cent of the college students studied suffered from headaches, with college and high school graduates running a close second; those with no schooling had the lowest percentage of headaches. When considering occupations, students had the highest percentage of headaches, followed closely by executives, professional people, and housewives. Those doing agricultural and manual work suffered the least from headaches. Tension headaches are described and illustrated, in addition to headaches due to high blood pressure, water retention, hangovers, and smoking. It is noted that 16.2 per cent of the nonsmokers had headaches compared to 8.6 per cent of the smokers. Indications for seeing the doctor about headaches are given, and a description of ergotamine-containing preparations as well as other medicines for the prevention and treatment of headache are included. Pain killers and other medicines used in order to obtain relief of symptoms are described. There is a chapter on miscellaneous methods of treating headaches, one on helpful hints for this condition, and the question of whether allergy is a factor in headache is fully described. The eyes as a cause of headache are covered in a separate chapter, as are ear, nose and throat disorders as a cause of headache. There is a chapter on special types of medical examinations and another on the mental or psychogenic treatment of headache. One chapter deals with the diagnosis and treatment of headache, if it is due to allergy. Some very important points are summed up in the last chapter, and a history form to be used by the doctor when asking the patient about headaches is included.

This is one of the most concise and authoritative books on headache written both to aid the layman in understanding his condition and to help the doctor in diagnosing and treating headaches. It should be a very useful brochure.—F.W.W.

ALLERGY IN CHILDHOOD. Jerome Glaser, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Pediatrician-in-Chief, Genesee Hospital, Consulting Pediatrician, Rochester General Hospital and St. Mary's Hospital, Rochester, New York. Publication No. 272, American Lecture Series, a monograph in the Bannerstone Division of American Lectures in Allergy. 529 pages, including index, illus. Springfield, Illinois: Charles C Thomas, 1956. Price $12.50.

At long last there is a much needed authoritative and complete book on pediatric allergy. Much of the material in Dr. Glaser's book is entirely new, and it contains special features of differential diagnosis and treatment of respiratory allergies and eczema in children.

Since the great majority of allergic children can be recognized at a very early age, the pediatrician skilled in the diagnosis of the diseases of infancy and childhood can detect the first evidences of allergic disease. The present day method of feeding almost all newborn infants results in a great variety of allergic manifestations. The early removal or abstinence from breast feeding and substitution of cow's milk offers a challenge to the pediatrician to cope with the early sensitization of infants to a variety of foods. He is also burdened with the responsibility of immunization problems, which are of particular importance in the allergic child.

The sixty-seven chapters and addenda indicate the many facets encountered in dealing with the allergic child in the light of our present knowledge of the subject, as compared with most books on adult allergy which neglect the very essence of allergy in early life.

There are fifteen chapters alone on the subject of dermatitis in infants and children, a subject of paramount importance in pediatric allergy. Allergy to insect bites and stings, drugs and vaccines, and their management, are considered in separate chapters. The symptomatic treatment of bronchial asthma contains prescriptions found to be effective as a result of the author's extensive experience. The several chapters on miscellaneous allergies alert the physician to the many special problems encountered in allergic children. Practical, effective elimination diets simplify the difficult problem of treating food allergies in children. In fact, every phase of the various factors influencing the allergic child is completely presented.

A fairly complete bibliography follows each chapter, and the addenda gives detailed instructions for the avoidance of various important environmental allergens. The photographs, both in color and black and white, on good paper stock, reflect the usual high standards of the publisher.

All physicians, whether in general practice or specializing in pediatrics and/or allergy, will find the book indispensable.—*F.W.W.*

ATOPIC DERMATITIS. Rudolf L. Baer, M.D. (editor), Associate Professor, Department of Dermatology and Syphilology, New York University Post-Graduate Medical School, and Skin and Cancer Unit and University Hospital, New York University-Bellevue Medical Center, New York, N. Y. Philadelphia: J. B. Lippincott Co., 1955. Cloth, 112 pages, illus. Price, $2.50.

Allergists who are not predominantly dermatologists will not agree with everything written by Dr. Baer (Editor) and his associates, Drs. M. B. Sulzberger, R. R. Kierland, A. Rostenberg, Jr., T. H. Sternberg and V. D. Newcomer, on the subject of atopic dermatitis. In successive chapters they discuss, respectively, the development of the concepts of atopic dermatitis (Baer): Its clinical and histological picture, certain stigmata associated with atopic dermatitis, a discussion of certain theories concerning its pathogenesis and, the management of atopic dermatitis.

Given the preferred term "atopic dermatitis" they stress the fact that in this disorder no agent, living or dead, organic or inorganic, has been incriminated or proven to be an "immediate cause." The disorder cannot be evoked in animals and in

humans, and in neither adults nor in children can exacerbations be produced during periods of remission.

On the basis of Tip's work showing that each of the syndromes, hay fever, bronchial asthma and atopic eczema, is governed by a pair of recessive genes, the hereditary factor seems certain. The known secondary factors are heat, cold, rapid change in temperature, perspiration, contact with silk or wool, the ingestion of specific foods and of groups of foods, and the application of greasy ointments. Psychogenic factors as nervous tension, over-exertion and excitement when associated with excessive perspiration also cause exacerbations, although soap, alkalis and certain types of medications are not mentioned. In this reviewer's experience, they also adversely affect the skin although tests have proved this not to be on the basis of contact dermatitis.

The skin of patients with atopic dermatitis is characterized by the fact that the sites of predilection are identical to those resulting from a "histamine flush," the temperature rising higher and remaining elevated longer than that noted in normal individuals. The patients also present a "white dermatographia" with the absence of flare in the triple-response following the intradermal injection of histamine. The patients' skins cool more quickly and warm more slowly than do those of normal individuals when they are placed respectively in cool and warm environments. The sites of predilection, however, warm more quickly in a given unit of time than those of normal non-atopic patients. The patients present a flat curve type of response in the glucose tolerance test. There is a tendency among them to hypotension.

The patients with atopic dermatitis can be recognized by other stigmata, namely, a sallow complexion with hyperpigmentation. They have ichthyoid skins with keratosis pilaris and partial anhydrosis.

Foods and inhalants may increase the pruritus, but their elimination does not clear the skin. The contributors to this volume disagree strongly with the frequently used statement that this disorder is due to "subcutaneous wheals" and that there is an antigen-antibody relationship following exposure to substances positive by skin tests.

General therapy is recommended, and consists of antimicrobial agents applied to combat local infection with steroid ointments used for temporary relief of inflammation and pruritus. The tranquillizing drugs should be used. Dietotherapy, although it is only rarely but then spectacularly successful, should be given a trial. The major and probably the most successful form of treatment is change in the environment to a warm, dry, or to a warm, moist, climate, depending on the type of dermatitis the patients present.—*E.A.B.*

ATLAS UND PRAKTIKUM DER DERMATOLOGIE UND VENEROLOGIE. W. Burckhardt, Professor-Poliklinik fur Haut-und Geschlechtskrankheiten, Zurich, Switzerland. 297 pages including index, with 65 black and white illustrations and 99 colored illustrations. New York: Intercontinental Medical Book Corp., 1955. Price $11.50.

Dermatologists speak a universal language, although they do not always agree on the terminology to be applied to some of the more obscure lesions they study. That the text of Burckhardt's dermatology and venereology is in German should discourage few, if any, prospective students in this field. Since Burckhardt writes clearly, the language is easily followed, especially since so much of it is of the technical type familiar to all physicians. The colored plates printed by von Zollikofer in Switzerland are among the finest available. The black and white illustrations are excellent.

The American reader will value the book as an atlas. He will not always agree with the terminology, as for instance, neurodermatitis and endogenous eczema. He

will certainly not agree with the prescription of arsenic as Fowler's Solution in eczema of childhood. Cortisone is mentioned only twice, once for the treatment of pemphigus and again for eczema.

On the other hand, Burckhardt treats atopic eczema of childhood with intravenous vitamin D and calcium gluconate twice daily. Sulfanilamide taken orally is used for the treatment of superficial infections. With this, few American dermatologists would agree.

But the treatment of the skin disorders listed is a minor part of the book. It will be difficult indeed to improve the illustrations and the text.—*E.A.B.*

ORIGINS OF RESISTANCE TO TOXIC AGENTS. Edited by M. G. Sevag, Roger D. Reid, and Orr E. Reynolds. Proceedings of the Symposium held in Washington, D. C. 471 pages with index. New York: The Academic Press, Inc., 1955. Price $12.00.

When, in 1928, penicillin was discovered, and soon afterwards the sulfonamides, it appeared as though we were on the brink of a new age. We would soon have other bacteriocides, virucides and substances available against a host of invading organisms and parasites afflicting humans, domestic animals and food crops. Although the illnesses we were treating had been growing less common and less severe for many years, the curves of morbidity and mortality took precipitous dips. All recoveries were in any case credited to the microbicides and all deaths occurred despite them. But the natural orders of biologic relationships established for some billions of years were not however, easily changed.

Patients began to react sometimes with simple discomfort and often with a spectrum of the most complex signs and symptoms of many types of toxicity, idiosyncrasy, intolerance and allergy. And the offending organisms, in their own way, appear to offer some resistance toward being wiped out. What had not been foreseen was, that with the lessening in numbers of the pathogenic bacteria there might be an increase and, as well, a capacity for invasion and the development of pathogenicity and toxins by organisms normally present and usually considered harmless. This so-called "superinfection" was often more severe than the original illness and sometimes killed the patient.

An attempt to solve these problems required experts in a number of associated disciplines. Dr. Sevag and his co-editors surveyed the subject matter "beforehand in its entirety," and formulated theorems. "These were divided into major component parts, each with as many subdivisions as there were questions in regard to unsolved and incomplete problems." The outlines were distributed to the twenty-eight principal speakers and moderators months before the meeting.

Discussed first was the question of resistance to microbicides, and second, resistance to herbicides and insecticides. A third session was devoted to drug tolerance, addiction and alcoholism, and a fourth to resistance factors, infectious agents and cancer cells. The last concerned itself with physiology and with hemical and genetic viewpoints.

It appears from the discussion that there is an antimony; that is, a contradiction between two principles each of which cannot be wholly true. If diseases are going to be "wiped out" but bacteria grow more "resistant," do these bacteria "mutate" to become resistant or do they "adjust" to an environment changed in that it now contains an antimicrobicide? The last is really our chief interest in the origins of resistance to toxic agents. Where is the dichotomy?

When bacteria become "resistant," are these new organisms the result of adaptation, genetic in type? If so, we must believe that we have under observation active mutation and selection in the respective Lamarkian and Darwinian senses of the

(Continued on Page A-36)

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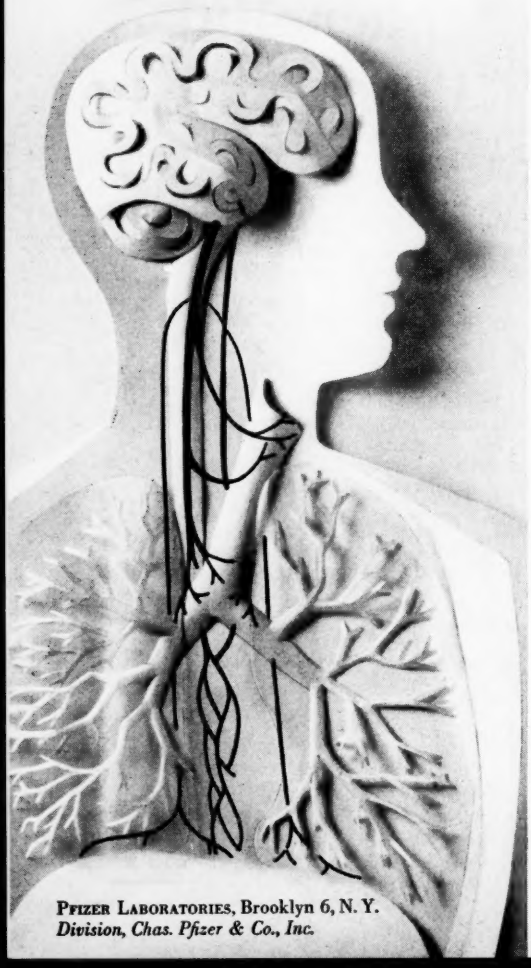

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(Continued from Page 232)

words. If, however, the bacteria become resistant because of built-in enzyme systems capable of sustaining life in the presence of the toxic agent, we are faced with a process of adaptation, truly physiologic in origin, that is, phenotypic.

Some toxic drugs as, for instance, the nitrogen mustards, can produce proven bacterial mutations. Others, of which penicillin is an example, can stimulate some bacteria to synthesize penicillinase which nullifies the effects of penicillin.

Bryson points out that organismal resistance may apparently occur by any one process or a combination of six processes. Since bacteria reproduce with great rapidity and, given adequate sustenance, are potentially immortal, their colonies contain tens, hundreds and thousands of billions or trillions. Under these circumstances, there may be present one spontaneous mutant which would survive an exposure which would kill its nonmutant kin. Its reproduction results immediately and with no phenomic lag in a colony of resistant organisms. But, since all of the nonresistant bacteria are not all equally exposed to the toxic agent, a second mechanism may come into play, namely, spontaneous mutation and selection but with a phenomic lag of one generation. If the toxic drug is a mutogen, then the resistance may be due to a mutated organism. In some cases the mutative drug may induce mutations in some of the bacteria and the capacity to mutate in others. There is then a lag of one generation for the second group of organisms.

Another possibility envisages a large number of simultaneously occurring phenotypic changes. The past pattern is similar, except that the spontaneous mutants occur after (not before) the toxic agent is added.

It is generally known (although the populations with which we are concerned number in the trillions), that mutations are rare and usually pathologic in nature; that is, harmful to the organism. That

such mutations should occur similarly and simultaneously both in the laboratory and in sick patients, and yet always move in the same direction, seems to many observers to border on the incredible.

Mitchell says, "The ability to mutate and thus give rise to heritable changes is a characteristic of all living cells. Mutation occurs spontaneously but its frequency can be influenced enormously by changes in environment, changes that may be imposed externally, as by radiation or chemical treatments, or internally, as by the acquisition of mutator genes or perhaps even by accumulations of metabolites. After mutation has taken place in a cell, a readjustment in relation to the environment is demanded, and the process of selection begins. If the readjustment is required is beyond the overall inherent biochemical capacity of the cell, then it will die. On the other hand, mutation in a cell may give it a superior capacity to survive in an existing environment and it and its descendants will be selected in favor of the parenteral type. Certainly all degrees of selection pressures intermediate between these extremes exist. These are all well-known facts and, in the present discussion of the relation of drug action to genetic factors, the drug constitutes an externally imposed environmental change."

Sevag, however, says, "The question is whether environmental chemical or physiochemical factors can induce the phenomena of tolerance." Some investigators boldly declare that hereditary changes occur by spontaneous gene formation independent of any environmental influences. He feels that these investigators have not given us a clear definition of what they mean by "spontaneous mutation." He believes that the mechanism underlying "spontaneous mutation" is not basically different from that which is implied by the term "chemical induction." He does not believe that "the changes can be attributed to an error in the function of a gene exclusive of endogenous or external inhibitory influences."

He states that, "the postulate that a gene can acquire all the required factors

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1. Wolfson, W. Q.: Mississippi Valley M. J. 77: 66, 1955.

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for its multiplication from its surroundings and can regulate the enzyme functions in the nucleus or cytoplasm or both and remain insusceptible to adverse changes within its circle of activities cannot be reconciled with the principles of chemistry."

He then proposes a concept that "the direct action of drugs, radiations and endogenous metabolic inhibitors on sensitive cells and cells that have acquired resistance induces in the protein molecules *configurational modifications,* or *deformations,* or *"paralysis."* This may just as well be true of human tissue cells as of bacteria.

The relationships of these altered states to eighteen basic theorems is then drawn. He ends with the note that, since *in vitro* control of nutritional components of the growth medium has made possible the prevention of the emergence of drug-resistant cells, these successes "may be indicative of potentialities for achieving similar successes in medical practice."—*E.A.B.*

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